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"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOL. XXX, No. 5 MAY 1958

EDITORIAL

A NEW CHAIR IN ANAESTHESIA

JACK'S beanstalk could hardly claim a more virile and rapid growth than the progress of anaesthesia in Great Britain during the last decade or so. We are told that the crowning glory of the beanstalk was a giant's castle, balanced, one has always felt, somewhat precariously on the upper foliage.

It does not perhaps require a great stretch of the imagination to see the parallel in the new Research Department of Anaesthetics in the Royal College of Surgeons. This, too, is situated at a considerable height, but not precariously, for the trunk and roots supporting it are indeed sound. Those who have visited the Department cannot have failed to enjoy the glorious vista of London which the balcony provides. In the coming summer one can envisage the staff from that high point of vantage probing the very depths of the problems of anaesthesia and then turning their glance upwards in philosophical contemplation, exploring the very meaning of man's consciousness.

The influence of this department must be increased by the offer of the British Oxygen Company to endow within the Royal College of Surgeons a Chair of Anaesthesia, to which purpose they are donating the sum of £150,000.

Many anaesthetists may consider that the business and wealth of this benefactor of the College are founded on the sale of medical gases, and it would seem not unnatural therefore that this company should make such a munificent gesture. The facts, of course, are very different. The medical section is a comparatively small part of that vast concern which we know as the British Oxygen Company. However, every member of the community both medical and non-medical, stands to benefit from the research carried on in the College Department, and it would be the wish of all to join in congratulating the company on its decision to donate some of its earnings to the benefit of the health of the country and indeed, as medicine knows no boundaries, of the world.

Brit. J. Anaesth. (1958), **30**, 206

THE INFLUENCE OF CARBON DIOXIDE ON THE NEUROMUSCULAR BLOCKING ACTIVITY OF RELAXANT DRUGS IN THE CAT

BY

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SHORTLY after the introduction of relaxants into routine anaesthetic practice Brennan (1952) observed that their action could be prolonged if the patients were over-ventilated. Clinical experience suggested that the converse might also be true, namely that when carbon dioxide was allowed to accumulate relaxation might be more difficult to obtain. To test the validity of this impression the experiments to be described were carried out.

METHOD

The sciatic nerve tibialis anterior muscle preparation in the intact cat (Brown, 1938) was used to assess the response of the muscle to known doses of relaxant in the presence of varying concentrations of carbon dioxide.

Healthy but otherwise unselected cats were used. After induction with ethyl chloride and ether, the right external jugular vein was cannulated and chloralose (80 mg/kg) given intravenously to maintain anaesthesia. Thereafter a tracheal cannula was inserted and artificial respiration established by means of a positive pressure respirator. This technique was employed to avoid the risk of hypoxia during the action of the relaxant and to facilitate the administration of carbon dioxide.

The sciatic nerve was exposed through a longitudinal incision on the posterior aspect of the thigh. It was crushed as far proximally as possible and ligated; its medial division was treated likewise. The tendon of the tibialis anterior muscle was attached to a flat steel spring myograph recording on a smoked drum. The stimulus was a square wave pulse of 0.5 m.sec duration applied to the sciatic nerve through shielded platinum electrodes at 10-sec intervals, strength 1 to 3 V.

It was intended to administer a given dose of relaxant and to compare the effect produced when the same dose was given during exposure to varying concentrations of carbon dioxide. Before this could be done it was necessary to know the effect of carbon dioxide on muscle contraction without the intervention of neuromuscular blocking agents. It was further required that the dose given and the effect produced could be measured accurately. For this purpose a divided dose technique suggested by Paton (personal communication) was adopted. In each instance a preliminary trial dose of relaxant was given to assess the approximate amount of drug required. The maximum depression of twitch without actual abolition was the objective.

The effect of three different concentrations of carbon dioxide on the action of four separate drugs was assessed. The concentrations of gas employed were 5, 10 and 20 per cent and the drugs used were suxamethonium, decamethonium, gallamine and tubocurarine.

A control series of injections of relaxants was given intravenously while the animals were ventilated with air. In a few instances oxygen was substituted for air to exclude any possible effect of the oxygen in the carbon dioxide/oxygen mixture. When the muscle twitch appeared to have recovered the appropriate mixture of carbon dioxide and oxygen was administered. The duration of exposure to carbon dioxide varied between 20 and 45 mins before the second series of injections was given, after which the carbon dioxide was discontinued. After recovery from the effects of the gas a third series of injections was given. The time interval between each series was the same and the dosage and number of injections were unaltered.

In three cats subtotal neuromuscular block was obtained by means of a continuous infusion of

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suxamethonium chloride. After establishing a satisfactory control period carbon dioxide was given; a different concentration to each cat.

In one group of seven cats the plasma potassium levels were estimated using the Eel flame photometer. In a second group of nine cats blood pH was measured continuously. For this purpose an artificial arteriovenous fistula was created by inserting a small glass chamber (capacity 3 ml) between the femoral artery and a superficial vein. This chamber contained both the measuring and reference electrodes which were connected to a Pye universal pH meter.

RESULTS

In the majority of cases the height of the muscle twitch was diminished when carbon dioxide was inhaled. In no instance was the twitch increased. Figure 1 illustrates the depression of muscle twitch obtained with different concentrations of carbon dioxide inhaled for varying periods.

Suxamethonium Chloride.

Initial injections of suxamethonium chloride increased the height of the individual twitches obtained by supramaximal shocks applied to the nerve. Further injections depressed the twitch and these injections were repeated at minute intervals until approximately 90 per cent block had been achieved. Recovery of the twitch after the last injection was rapid and frequently rose, temporarily, above the control level. Despite this apparent recovery a delay of 30 minutes at least was required between each series of injections to avoid cumulative effects.

Invariably the effect of the administration of carbon dioxide was to lessen the block. The temporary nature of the resistance to suxamethonium produced by carbon dioxide is demonstrated by the return of nearly complete block after the animal has been ventilated with air. The extent, duration and variation of the response is illustrated in figures 2, 3 and 4 and the effects of carbon dioxide on a group of nine cats given suxamethonium are outlined quantitatively in table I.

The use of a continuous infusion of suxamethonium provided a more accurate picture of the course of the resistance to the drug produced by carbon dioxide. Reference to figure 5 shows that

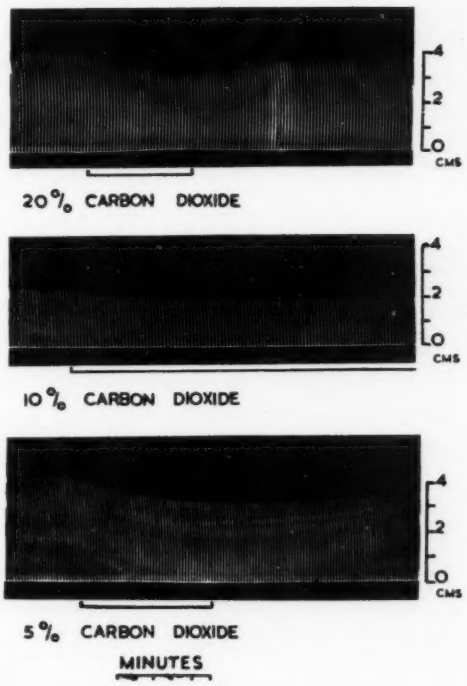

FIG. 1

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The illustrations show the depression in the size of the muscle twitch obtained by exposure to different concentrations of carbon dioxide.

TABLE I

Percentage change in the size of the tibialis anterior muscle twitch obtained after equal doses of suxamethonium before, during and after the administration of carbon dioxide.

% Carbon dioxide	Dose in μg/kg	Percentage depression		
		Control	CO_2 effect	Recovery
5	5 × 10	81	36	75
	4 × 10	89	70	98
	3 × 20	98	91	98
10	5 × 10	69	8	70
	3 × 10	97	67	97
	3 × 10	99	65	99
20	3 × 20	97	88	97
	6 × 20	50	30	39
	5 × 10	95	12	94

antagonism began to develop as soon as the animal was exposed to 10 per cent carbon dioxide and reached its peak within 20 minutes. Immediately the carbon dioxide was discontinued the resistance to suxamethonium weakened perceptibly but the return of subtotal neuromuscular block was a gradual process and nearly 45 minutes elapsed before the control level was reached. Exposure to 5 and 20 per cent carbon dioxide produced essentially similar results.

Gallamine Triethiodide.

In nine cats given gallamine in divided doses neuromuscular block was obtained in each case without initial stimulation although some increase in the size of the twitch was noted for a brief period after the first injection in many of the experiments. This was not observed after any

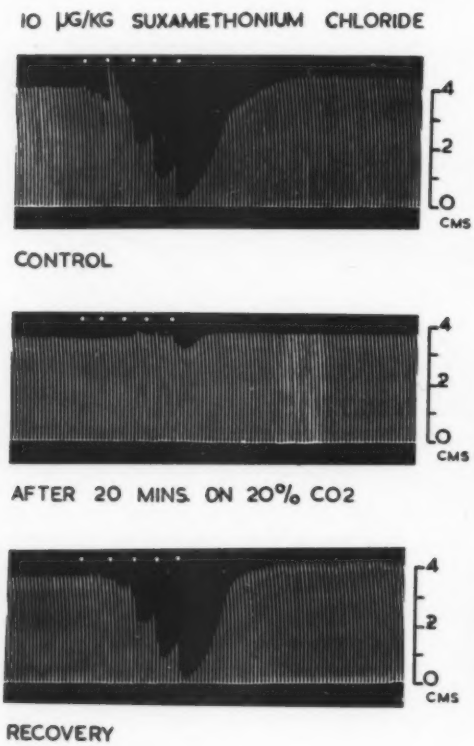

FIG. 2

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The upper tracing shows the depression, after initial stimulation, in muscle twitch achieved by five intravenous injections of suxamethonium chloride (20 µg/kg). The middle tracing shows the resistance of muscle activity to the same dose of suxamethonium during exposure to 20 per cent carbon dioxide. The lower tracing shows the effects of the same dose of suxamethonium after the animal has been allowed to recover from exposure to carbon dioxide. The interval between each series of injections was 45 minutes.

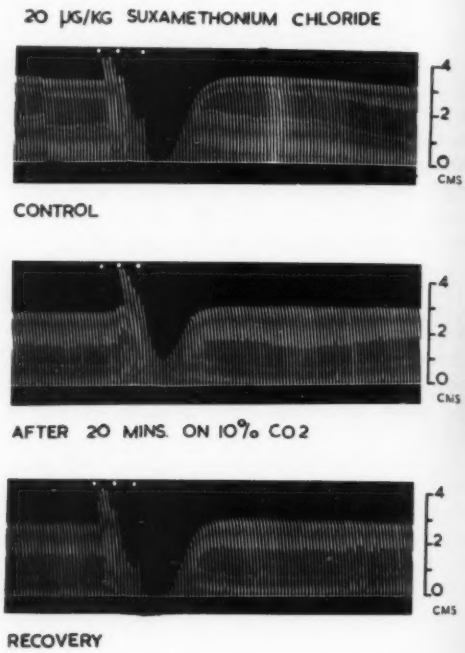

FIG. 3

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The upper tracing shows the depression, after initial stimulation, in muscle twitch achieved by three intravenous injections of suxamethonium chloride (20 µg/kg). The middle tracing shows the resistance of muscle activity to the same dose of suxamethonium during exposure to 10 per cent carbon dioxide. The lower tracing shows the effects of the same dose of suxamethonium after the animal has been allowed to recover from exposure to carbon dioxide. The interval between each series of injections was 45 minutes.

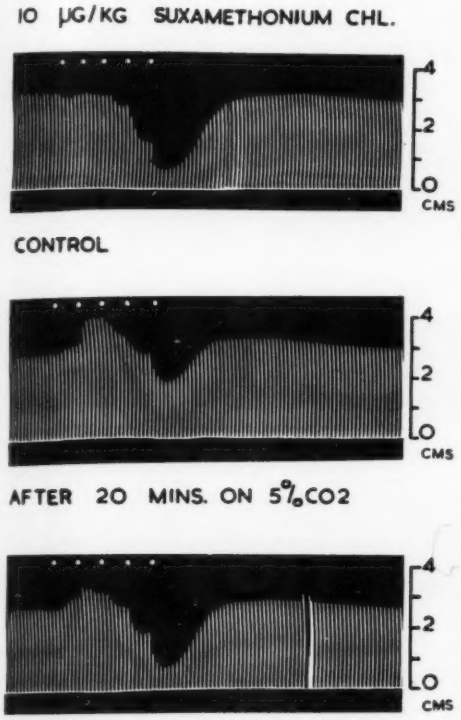

FIG. 4

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The upper tracing shows the depression in muscle twitch achieved by five intravenous injections of suxamethonium chloride (10 µg/kg). The middle tracing shows the resistance of muscle activity to the same dose of suxamethonium during exposure to 5 per cent carbon dioxide. The lower tracing shows the effects of the same dose of suxamethonium after the animal has been allowed to recover from exposure to carbon dioxide. The interval between each series of injections was 45 minutes.

succeeding injection even when recovery from previous doses appeared complete. In each experiment the inhalation of carbon dioxide increased resistance to neuromuscular block with gallamine. The extent of this resistance is illustrated in figures 6, 7 and 8 and table II gives the percentage change in the size of the twitch obtained after equal doses of gallamine before, during and after the administration of carbon dioxide.

TABLE II

Percentage change in the size of the tibialis anterior muscle twitch obtained after equal doses of gallamine before, during and after the administration of carbon dioxide.

% Carbon dioxide	Dose in mg/kg	Percentage depression		
		Control	CO_2 effect	Recovery
5	2 × 0.5	64	19	51
	2 × 0.5	92	61	88
	2 × 0.5	98	67	97
10	2 × 0.5	88	37	83
	2 × 0.5	96	43	96
	2 × 0.5	99	28	99
20	1 × 0.5	91	20	76
	1 × 0.5	69	55	61
	4 × 0.5	97	47	98

Decamethonium.

The development of neuromuscular block with decamethonium closely followed the pattern described for block with suxamethonium. The initial stimulation, however, was more marked, as shown in figures 9, 10 and 11 and both muscle fasciculation and fibrillation were more prominent. As before, exposure to carbon dioxide antagonized the effect of the relaxant and the extent of this resistance in six cats is set out in table III.

TABLE III

Percentage change in the size of the tibialis anterior muscle twitch obtained after equal doses of decamethonium before, during and after the administration of carbon dioxide.

% Carbon dioxide	Dose in µg/kg	Percentage depression		
		Control	CO_2 effect	Recovery
5	3 × 5	100	83	91
	1 × 10			
	1 × 5	94	87	94
10	2 × 10	94	40	81
	4 × 5	97	83	97
20	2 × 5	100	0	86
	3 × 5	100	32	100

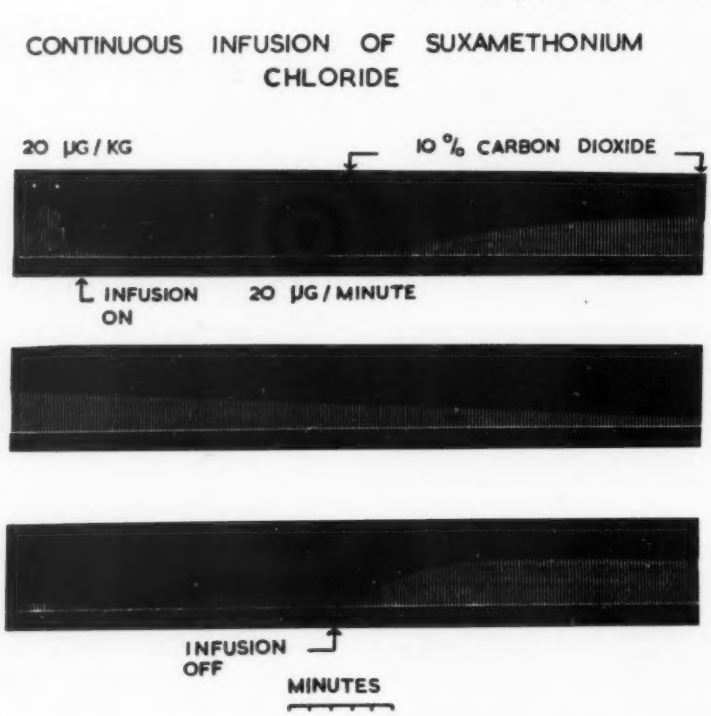

FIG. 5

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The neuromuscular block has been achieved by the continuous infusion of suxamethonium chloride. The animal was then ventilated with 10 per cent carbon dioxide and the antagonism to neuromuscular block which developed is shown, as is also the return of neuromuscular block when the carbon dioxide was discontinued.

Tubocurarine Chloride.

Tubocurarine was given in divided doses to a group of six cats. In these experiments exposure to carbon dioxide enhanced the neuromuscular blocking properties of the drug as shown in figures 12, 13 and 14. The increase in neuromuscular block obtained is shown quantitatively in table IV.

Plasma Potassium.

No consistent trend was shown in the plasma potassium levels during exposure to carbon dioxide, but during recovery from the effects of the gas it was observed that the level rose in each instance. The smallest increase was 0.4 m.equiv/l. and the largest 1.8 m.equiv/l. The average in seven cats was 0.97 m.equiv/l.

TABLE IV

Percentage change in the size of the tibialis anterior muscle twitch obtained after equal doses of tubocurarine, before during and after the administration of carbon dioxide.

% Carbon dioxide	Dose in µg/kg	Percentage depression		
		Control	CO_2 effect	Recovery
5	2 × 100	53	94	69
	2 × 100	62	90	83
10	2 × 200	43	81	67
	2 × 200	39	42	33
20	3 × 100	63	87*	53
	1 × 100	91	100	97
	1 × 50			

* Dose: 2 × 100 µg/kg

3 INJECTIONS OF 5 µg/kg DECAMETHONIUM
4 INJECTIONS OF 5 µg/kg DECAMETHONIUM
3 INJECTIONS OF 5 µg/kg DECAMETHONIUM

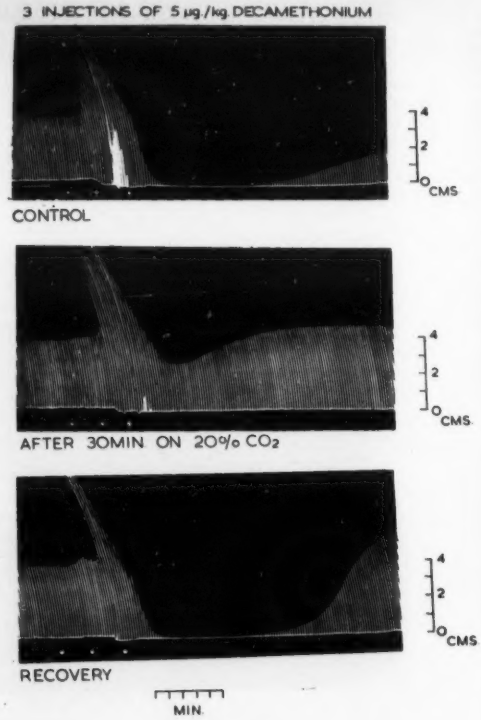

FIG. 6

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The upper tracing shows the initial stimulation followed by depression achieved by three injections of decamethonium (5 µg/kg). The middle tracing shows the resistance of muscle activity to the same dose of decamethonium during exposure to 20 per cent carbon dioxide. The lower tracing shows the effects of the same dose of decamethonium after the animal has been allowed to recover from exposure to carbon dioxide. The interval between each series of injections was 60 minutes.

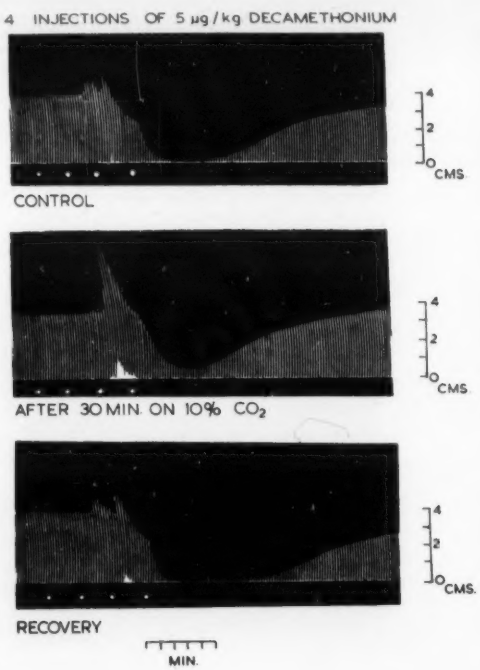

FIG. 7

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The upper tracing shows the depression, after initial stimulation, in muscle twitch achieved by four injections of decamethonium (5 µg/kg). The middle tracing shows the resistance of muscle activity to the same dose of decamethonium during exposure to 10 per cent carbon dioxide. The lower tracing shows the effects of the same dose of decamethonium after the animal has been allowed to recover from exposure to carbon dioxide. The interval between each series of injections was 60 minutes.

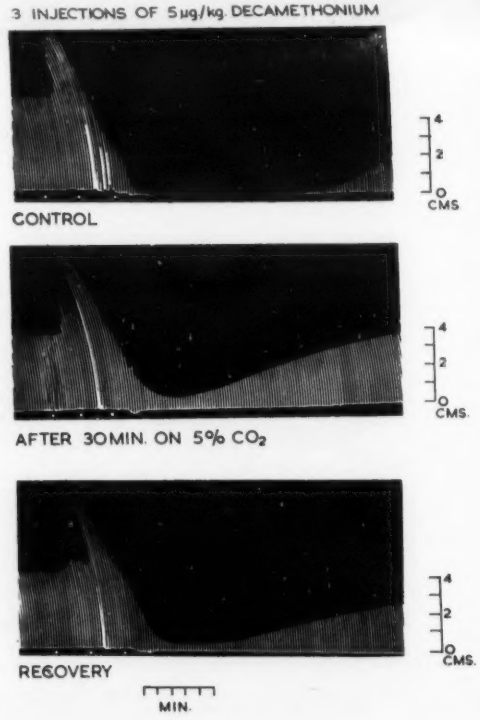

FIG. 8

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The upper tracing shows the depression in muscle twitch obtained by three intravenous injections of decamethonium (5 µg/kg). The middle tracing shows the resistance of muscle activity to the same dose of decamethonium during exposure to 5 per cent carbon dioxide. The lower tracing shows the effects of the same dose of decamethonium after the animal has been allowed to recover from exposure to carbon dioxide. The interval between each series of injections was 60 minutes.

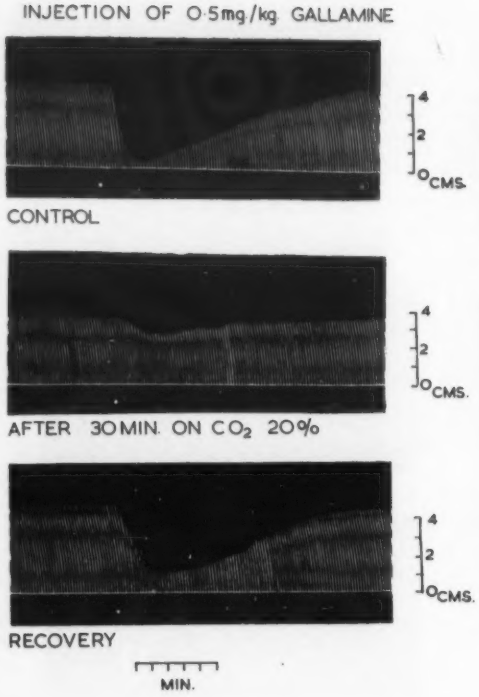

FIG. 9

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The upper tracing shows the depression in muscle twitch achieved by one intravenous injection of gallamine (0.5 mg/kg), without initial stimulation. The middle tracing shows the resistance of muscle activity to the same dose of gallamine during exposure to 20 per cent carbon dioxide. The lower tracing shows the effects of the same dose of gallamine after the animal has been allowed to recover from exposure to carbon dioxide. The interval between each series of injections was 60 minutes.

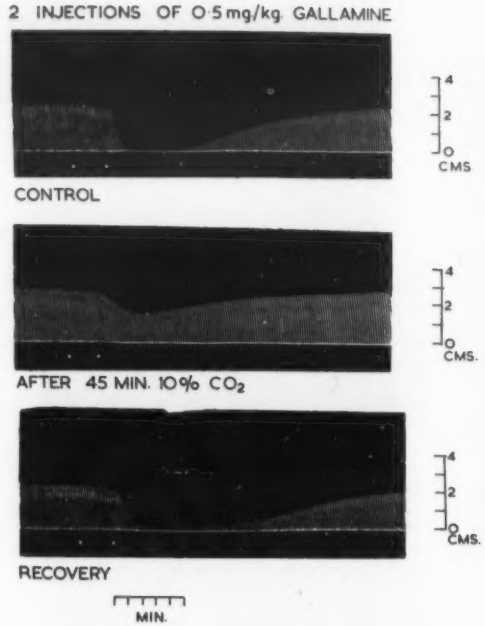

FIG. 10

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The upper tracing shows the depression, without initial stimulation, in muscle twitch achieved by two intravenous injections of gallamine (0.5 mg/kg). The middle tracing shows the resistance of muscle activity to the same dose of gallamine during exposure to 10 per cent carbon dioxide. The lower tracing shows the effects of the same dose of gallamine after the animal has been allowed to recover from exposure to carbon dioxide. The interval between each series of injections was 60 minutes.

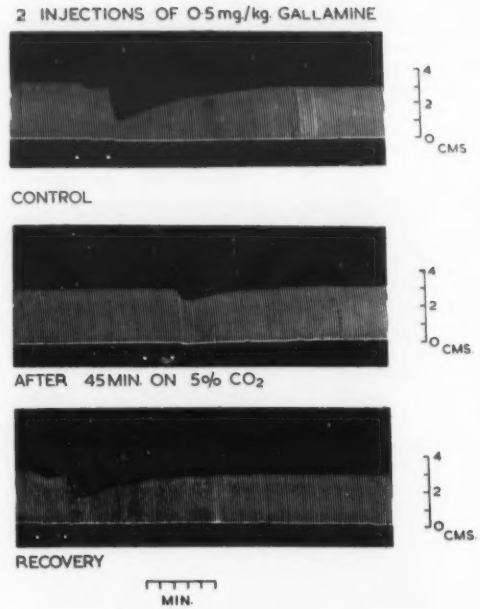

FIG. 11

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The upper tracing shows the depression, without initial stimulation, in muscle twitch achieved by two intravenous injections of gallamine (0.5 mg/kg). The middle tracing shows the resistance of muscle activity to the same dose of gallamine during exposure to 5 per cent carbon dioxide. The lower tracing shows the effects of the same dose of gallamine after the animal has been allowed to recover from exposure to carbon dioxide. The interval between each series of injections was 60 minutes.

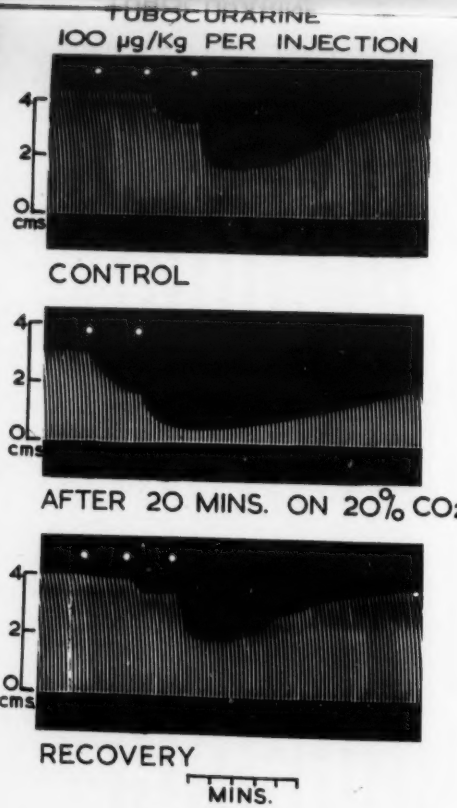

FIG. 12

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The upper tracing shows the depression, without initial stimulation, in muscle twitch achieved by three intravenous injections of tubocurarine (100 µg/kg). The middle tracing shows the marked depression achieved by only two injections during exposure to 20 per cent carbon dioxide. The lower tracing shows the effects of the original dose of tubocurarine after the animal has been allowed to recover from exposure to carbon dioxide. The interval between each series of injections was 60 minutes.

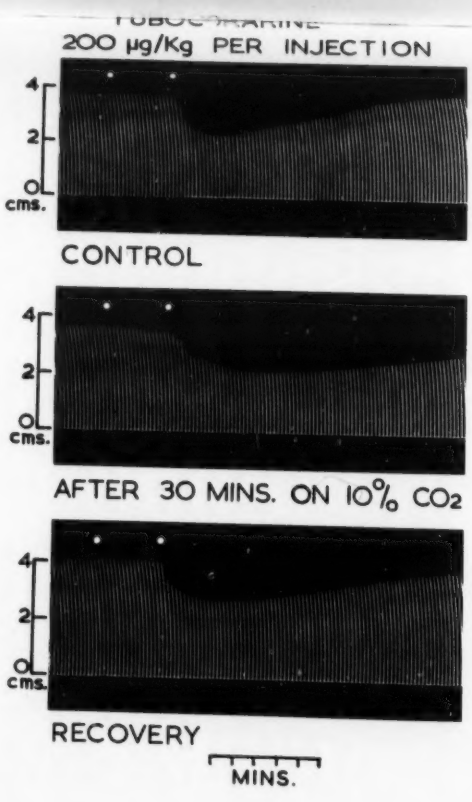

FIG. 13

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The upper tracing shows the depression, without initial stimulation, in muscle twitch achieved by two injections of tubocurarine (200 µg/kg). The middle tracing shows the increased depression of muscle activity by the same dose of tubocurarine during exposure to 10 per cent carbon dioxide. The lower tracing shows the effects of the same dose of tubocurarine after the animal has been allowed to recover from exposure to carbon dioxide. The interval between each series of injections was 60 minutes.

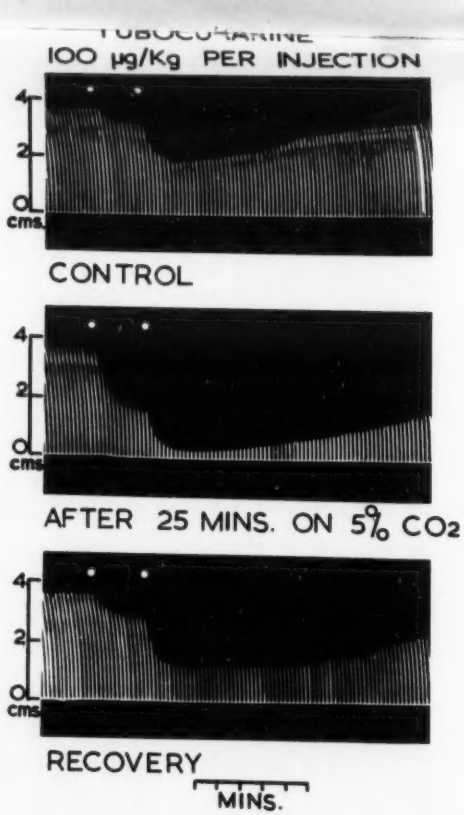

FIG. 14

Sciatic nerve tibialis anterior muscle preparation in the intact cat. The upper tracing shows the depression, without initial stimulation, in muscle twitch achieved by two injections of tubocurarine (100 µg/kg). The middle tracing shows the increased depression of muscle activity by the same dose of tubocurarine during exposure to 5 per cent carbon dioxide. The lower tracing shows the effects of the same dose of tubocurarine after the animal has been allowed to recover from exposure to carbon dioxide. The interval between each series of injections was 60 minutes.

Blood pH.

The blood pH value invariably fell on exposure to carbon dioxide. The range of this fall was 0.2 to 1.0 pH units and the average was 0.5 units. The rate and extent of the fall were directly related to the concentration of carbon dioxide employed; the higher the concentration the greater the effect.

DISCUSSION

The ability of carbon dioxide to modify the response of the tibialis muscle to single nerve stimuli is not difficult to explain. The general narcotic effect of carbon dioxide has been recognized for many years, indeed Hickman employed the gas to produce anaesthesia in animal experiments in about the year 1820, and more recently Waters (1937) used a 30 per cent concentration for anaesthetic purposes in clinical practice. More specifically Waller (1895) found that carbon dioxide interfered with neural transmission and later Lorente de No (1946) showed that when an isolated nerve was exposed to an environment of 5 per cent carbon dioxide its threshold for stimulation was raised. The depression of the muscle twitch, therefore, could reasonably have been anticipated.

The ability to alter the neuromuscular blocking action of different drugs is less easy to explain. There is a possibility that carbon dioxide modifies enzyme activity and it has even been suggested that it acts as a physiological anticholinesterase (Gesell et al., 1944). Normally the brief action of suxamethonium is due to its rapid destruction by the enzyme pseudocholinesterase and only slightly to its excretion unchanged in the urine. The reduced effectiveness of a given dose of suxamethonium in the presence of carbon dioxide could be due to its more rapid destruction by more efficient enzyme action. But the optimum pH for pseudocholinesterase activity is 8.5 (Augustinsson, 1948), and in these circumstances potentiation rather than antagonism of the neuromuscular block could be expected if there were no other factors to be considered. Support for the anticholinesterase theory could be derived from the resistance to neuromuscular block with gallamine produced by carbon dioxide. For this theory to be acceptable, however, tubocurarine ought also to be antagonized. The fact that the action of tubocurarine is enhanced in the presence of carbon dioxide would seem to exclude this explanation.

Although only 5 to 15 per cent of suxamethonium is excreted through the kidneys (Norton and de Beer, 1954) the excretion of the other relaxant drugs is mainly renal. For this reason factors which modify renal blood flow have to be considered. The accumulation of carbon dioxide in the blood reduces renal blood flow and consequently relaxant drugs tend to be retained. Their action, theoretically, should be enhanced in these circumstances, but this is only true of tubocurarine. The influence of renal blood flow can therefore probably be disregarded.

The anticurare action of potassium was described by Wilson and Wright (1936), and two years later Catell and Civin (1938) showed that the inhalation of a 10 per cent concentration of carbon dioxide produced a temporary rise in blood potassium in cats. This rise, however, was not sustained and fell again even while the animal continued to breathe the gas. The observation of Catell and Civin was confirmed by Mackay in 1947, who claimed that the rise in serum potassium reached a peak about the fifth minute and gradually returned to normal within 30 minutes; when the carbon dioxide was discontinued there was a further secondary rise in serum potassium. This postinhalation rise was also observed by Brown (1955) in experiments on dogs, but he was unable to show a fall in serum potassium after the initial rise during the administration of carbon dioxide.

In the present series of experiments there was a gradual rise often preceded by a slight fall in serum potassium during the administration of carbon dioxide which continued for some considerable time after the administration of the gas ceased, whereas the resistance to neuromuscular block began to diminish immediately the carbon dioxide was discontinued (fig. 4). It is obvious, therefore, that there is no direct relationship between serum potassium levels and resistance to relaxants, a fact emphasized by the work of Davis et al. (1955). These workers concluded that, despite the known antagonism of potassium to suxamethonium, the inhalation of carbon dioxide by dogs given this drug prolonged the duration of muscle weakness. The failure of carbon dioxide

to reduce the activity of tubocurarine is further evidence that potassium is unlikely to be involved.

As well as potassium, adrenaline is readily released by carbon dioxide and its ability to support neuromuscular activity is well known. But again the enhanced activity of tubocurarine in the presence of carbon dioxide would seem to exclude any adrenaline influence.

Among the many factors that influence biological activity the degree of ionization is recognized to be particularly significant (Albert, 1952). Its importance is due to the fact that the molecules and corresponding ions of many drugs behave differently; some drugs are active in the molecular phase, others show activity only when ionized. These changes in ionization, however, are not confined to drugs; similar changes occur at the receptor sites in response to variations in the environmental pH.

In this series of experiments it has been shown that a change in blood pH follows ventilation with carbon dioxide and that this change is associated with an alteration in the response of the tibialis anterior muscle to relaxant drugs. Three of these drugs, suxamethonium, decamethonium and gallamine have pK_a values above 13 and are therefore completely ionized within the pH range employed. Tubocurarine, although containing "onium" groups in the same pK_a range, also contains two phenolic hydroxyl groups which have pK_a values of 8.1 and 9.1 (Kalow, 1954). Such values are susceptible to changes in blood pH and consequently variations in blood pH will alter their degree of ionization. This may explain why the action of tubocurarine differs from that of the other relaxants. Support for this explanation comes from the observation (Payne, 1958) that the neuromuscular blocking property of dimethyl tubocurarine, which does not contain hydroxyl groups, is antagonized in the presence of carbon dioxide.

Additional support is provided by the fact that the action of mecamylamine is also enhanced by exposure to carbon dioxide (Payne and Rowe, 1957). Mecamylamine with a pK_a value of 11.3 has a small but appreciable quantity in the unionized state in body fluids and like tubocurarine is susceptible to changes in blood pH (Milne et al., 1957). According to these authors the unionized component diffuses across cell membranes to combine with the intracellular protein and in this way a considerable quantity can be stored in tissues. A change in pH presumably upsets this balance as the inhalation of carbon dioxide leads to a rise in the plasma level of mecamylamine concomitant with a fall in tissue content (Payne and Rowe, 1957).

The combination of mecamylamine with cell proteins draws attention to another factor likely to influence the action of carbon dioxide on neuromuscular blocking agents. The effectiveness of drugs is often modified by the binding power of proteins. It is known that the intensity and duration of action of a given dose is inversely proportional to that fraction bound to protein and that alterations in plasma pH influence the ability of the plasma proteins to take up certain drugs (Goldstein, 1949). When carbon dioxide is inhaled the resulting rise in its tension in the blood raises the hydrogen-ion concentration. Such a reduction in pH may facilitate the combination of the quaternary ammonium salts with protein, thereby limiting their activity.

This would explain the resistance to suxamethonium, decamethonium and gallamine which develops in the presence of carbon dioxide without invalidating the explanation given for the enhanced activity of tubocurarine under similar conditions.

SUMMARY

Four series of experiments have been carried out to study the influence of carbon dioxide on the neuromuscular blocking properties of certain drugs. Under the conditions of the experiments carbon dioxide opposed the action of suxamethonium, decamethonium and gallamine but enhanced the activity of tubocurarine.

Concomitant studies on plasma potassium levels and blood pH values were carried out. No direct relationship could be shown between the plasma potassium levels and the modified activity of the relaxant drugs. There was, however, an invariable decrease of between 0.2 and 1 unit in the pH values which could be related to the change in response to these drugs.

No complete explanation could be given for the modified response to relaxants induced by carbon dioxide, but it is suggested that changes

in the degree of ionization and protein binding could be responsible.

ACKNOWLEDGMENTS

I am indebted to Professor W. D. M. Paton, F.R.S., for advice, criticism and facilities to carry out this work, and to Dr. J. R. Vane for many helpful suggestions.

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THE INFLUENCE OF CERTAIN GANGLIONIC BLOCKING AGENTS ON NEUROMUSCULAR TRANSMISSION

BY

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GANGLIONIC blockade was first used to produce controlled hypotension during surgery by Scurr (1951). This technique has since become generally accepted in anaesthetic practice.

Ganglion blocking drugs now available include the methonium compounds and the short acting agents trimetaphan and homatropinium (Trophenium).

There is no doubt that these drugs act selectively on the sympathetic ganglia, which is, perhaps, surprising in view of the similar humoral transmission mechanism thought to operate at other synapses and also at the motor endplates. Bülbring and Depierre (1949) suggested that the differences in the physiological mechanisms at sympathetic ganglia and the neuromuscular junction are quantitative rather than qualitative, and Paton (1954) considers the anatomical differences enough to account for dissimilarities in the actions of drugs at the two sites.

It seems likely that a drug which is active at sympathetic ganglia would, in sufficient concentration, be effective at the motor endplate (and vice versa).

The methonium compounds have been shown to have a neuromuscular blocking action in very large doses by Barlow and Ing (1948) and by Paton and Zaimis (1948). These workers showed that as the length of the chain between the quaternary nitrogen atoms decreases, so does the neuromuscular blocking effect diminish, being at its least in the hexane and pentane derivatives. However, large doses of hexamethonium will produce "head-drop" in the rabbit, and this effect is potentiated by curare.

With regard to trimetaphan, Acheson and Pereira (1946) stated that this drug had no curare-like effect. Randall et al. (1949) agreed with this observation and considered a slight muscular weakness noted in dogs to be due to the deficient blood supply caused by the hypotension. It is interesting to note that nearly all the animals which received a lethal dose of trimetaphan died of respiratory failure.

Tewfik (1957), noting a prolongation of suxamethonium apnoea in patients also receiving trimetaphan, suggested that trimetaphan has some slight muscle-paralyzing effect and may be destroyed by pseudocholinesterase. Payne (1957) has recently shown that trimetaphan has a weak neuromuscular blocking effect in cats previously given mecamylamine.

In the case of homatropinium, large doses are reported by Robertson et al. (1957) to produce respiratory paralysis in mice, rats, rabbits and cats. This may indicate the possibility of neuromuscular block occurring with this drug also.

Recent clinical experience has led us to believe that the effect of ganglion blocking drugs on neuromuscular transmission may be of practical importance. Accordingly, we decided to investigate and compare this effect in the case of hexamethonium, trimetaphan and homatropinium.

METHOD

The rat diaphragm preparation (Bülbring, 1946) was selected for this investigation. This provides a preparation of mammalian muscle which can easily be stimulated directly, or indirectly via the phrenic nerve. It may be studied under accurately controllable and reproducible conditions. Because of the large surface area and thin nature of the muscle, it is readily perfused and the effects of changes in the perfusion fluid are rapidly apparent.

Healthy, adult, albino rats were killed by a blow on the head and the diaphragm and phrenic nerves were removed. Each preparation consisted

of that part of the hemidiaphragm which is of costal origin, together with its phrenic nerve. This was perfused in 200 ml of Kreb's solution at 37°C, through which was bubbled a mixture of 95 per cent oxygen and 5 per cent carbon dioxide. The muscle was secured by its costal origin to an electrode. The insertion into the central tendon was fastened to a fine steel wire serving both as a second electrode and as attachment to a recording lever writing on a smoked drum. The phrenic nerve rested across another pair of electrodes. Both direct muscle stimulation via the first pair of electrodes and indirect (nerve) stimulation via the second pair of electrodes were effected by appropriate supramaximal, square-wave pulses at a frequency of 5 per minute.

In accordance with the object of this investigation, preparations of the drugs involved were those commonly used in anaesthesia.

Each ganglion blocking agent was investigated by three different experiments, as follows.

(1) *Effect of ganglion blocking agent alone.*

Uniform contractions of the muscle in response both to direct and to indirect stimulation were recorded. Then, during indirect stimulation (i.e. via the phrenic nerve), successive amounts of the drug under investigation were added to the perfusion bath so as to produce a progressive increase in concentration. Finally, direct muscle stimulation was applied in order to determine whether any effect produced by the drug was on the indirect response alone. During this final period of direct stimulation the drug concentration was further increased.

(2) *Effect of ganglion blocking agent plus curare.*

A fresh preparation was used. Partial curarization was effected before the drug under investigation was added. This same preparation was then thoroughly washed three times with fresh Kreb's solution and allowed to recover fully. Experiment 1 was then performed upon it, in order to establish that any difference in response had been due to the presence of curare and not to any peculiarity of the preparation.

(3) *Effect of Neostigmine on recovery from ganglion blocking agent.*

A preparation was exposed to a concentration of ganglion blocking drug sufficient to produce maximal response. It was then perfused in a lower concentration so that relatively slow recovery occurred. During this recovery phase indirect stimulation was applied and neostigmine was then added.

RESULTS

In untreated preparations it was found that uniform contractions resulted from both direct and indirect stimulation. Response to the former was greater than the response to the latter. This is usual with this preparation and the accepted explanation is as follows. Direct stimulation causes each muscle fibre to contract. The associated action potential traverses the fibre and excites the nerve fibrils of the motor endplate as it passes. A secondary response is produced and summation results in an increased contraction. Neuromuscular block will prevent this secondary effect from influencing the muscle fibre, and the observed twitch following direct stimulation is then comparable to that caused by indirect stimulation of an untreated (noncurarized) preparation.

All the drugs investigated modified the response of the preparation. The effects produced were as follows.

Hexamethonium bromide (fig. 1). 200 mg of this drug produced no effect. A further 100 mg produced a diminution of the twitch and a final 100 mg resulted in complete neuromuscular block. Direct stimulation still produced active contractions (reduced slightly to the level of the original indirect response, as explained above) and these were unaffected by two further 200 mg doses of hexamethonium.

Hexamethonium produced neither initial potentiation of the contractions nor spontaneous muscle twitches.

Hexamethonium plus curare (fig. 2). Two 0.1 mg doses of d-tubocurarine produced partial neuromuscular block. Following this, only 250 mg of hexamethonium (in divided doses) produced total block. It is interesting to note the initial anatagonism to curare produced by the first 100 mg dose of hexamethonium. After washing, this same preparation required a total of 375 mg of hexamethonium before total block was produced (fig. 3).

Hexamethonium plus neostigmine (fig. 10a). Neostigmine 1 mg assisted the recovery from

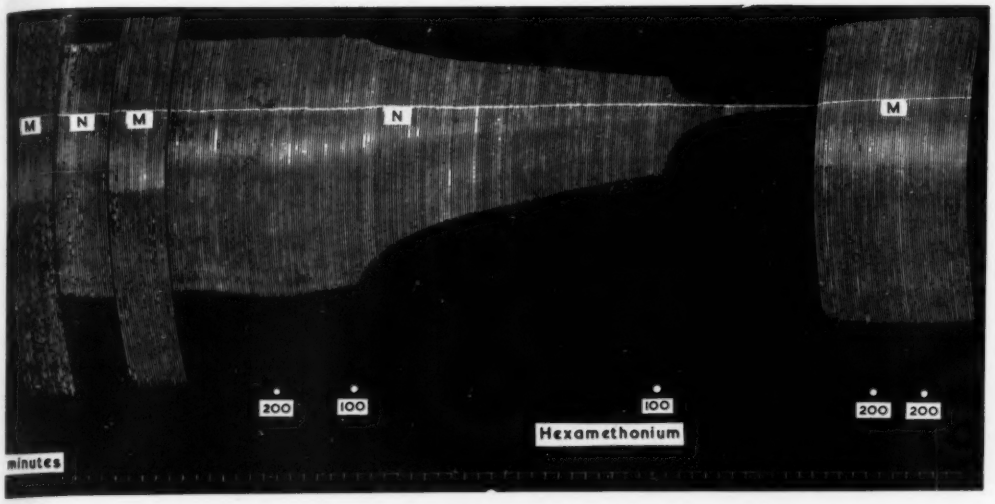


FIG. 1

Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation. N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.
Neuromuscular block produced by the addition of successive doses of 200 mg, 100 mg and 100 mg of hexamethonium. Direct stimulation still produces an active response, unaffected by two further 200 mg doses of hexamethonium.

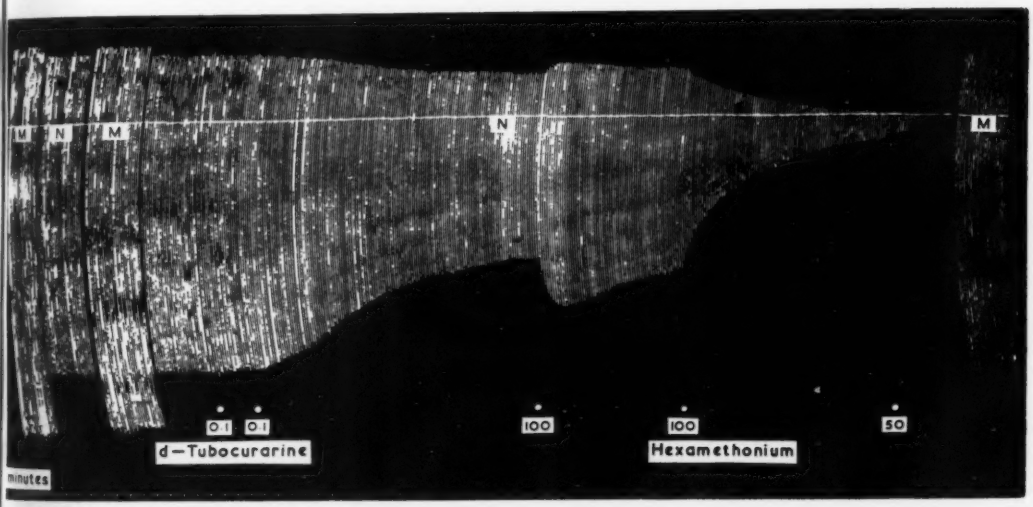


FIG. 2

Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation. N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.
Partial neuromuscular block produced by two 0.1 mg doses of d-tubocurarine. Complete block produced by subsequent doses of 100 mg, 100 mg and 50 mg of hexamethonium.

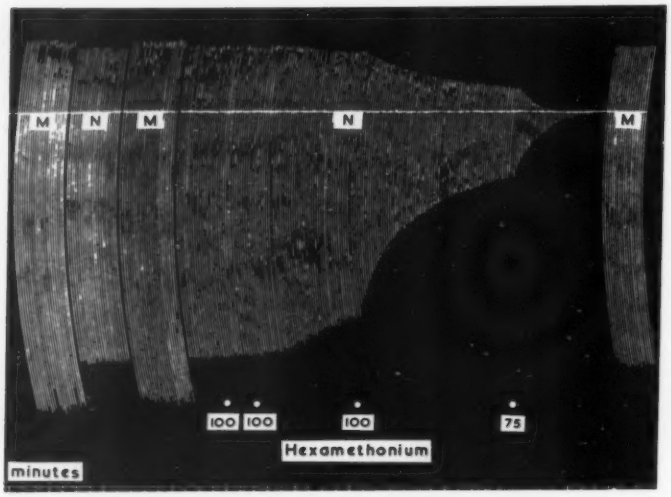


FIG. 3
Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation.
N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.
Same preparation as in figure 2 after washing and full recovery. Complete neuromuscular block after total of 375 mg of hexamethonium.

neuromuscular block produced by hexamethonium.

Trimetaphan (fig. 4). Two 20 mg doses produced no effect, but a third similar dose produced total neuromuscular block. As before, the direct response was also slightly reduced, but further doses of 20 mg and 40 mg had no effect on it. No initial stimulation or muscle fasciculation was seen with trimetaphan.

Trimetaphan plus curare (fig. 5). Following partial curarization, only 20 mg of trimetaphan produced total block. After washing, this same preparation required 60 mg of trimetaphan (in divided doses) before complete block occurred (fig. 6).

Trimetaphan plus neostigmine (fig. 10b). Neostigmine 1 mg increased the degree of neuromuscular block in a preparation recovering from trimetaphan.

Homatropinium (fig. 7). 20 mg had no effect. A further 20 mg produced total neuromuscular block. Again the direct response was slightly depressed, but was unaffected by a further 20 mg and 40 mg of homatropinium. No initial stimulation or muscle fasciculation occurred.

Homatropinium plus curare (fig. 8). Following partial curarization, only 20 mg of homatropinium produced total block. After washing, this same preparation required 40 mg of homatropinium to effect total block (fig. 9).

Homatropinium plus neostigmine (fig. 10c). Neostigmine 1 mg accelerated the recovery from total homatropinium block.

The above results are summarized in table I.

TABLE I
Summary of Results.

Drug	Dose producing total neuromuscular block		Effect of neostigmine on block
	Alone	After partial curarization	
Hexamethonium	400 mg (200 mg%)	250 mg (125 mg%)	Reversed
Trimetaphan	60 mg (30 mg%)	20 mg (10 mg%)	Potentiated
Homatropinium	40 mg (20 mg%)	20 mg (10 mg%)	Reversed

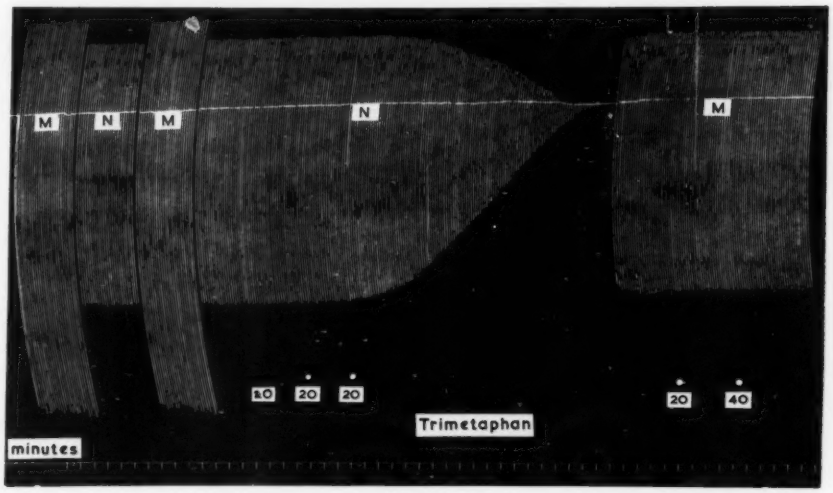


FIG. 4

Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation. N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.
Neuromuscular block produced by three 20 mg doses of trimetaphan. Direct stimulation still produces an active response, unaffected by a further 20 mg and 40 mg of trimetaphan.

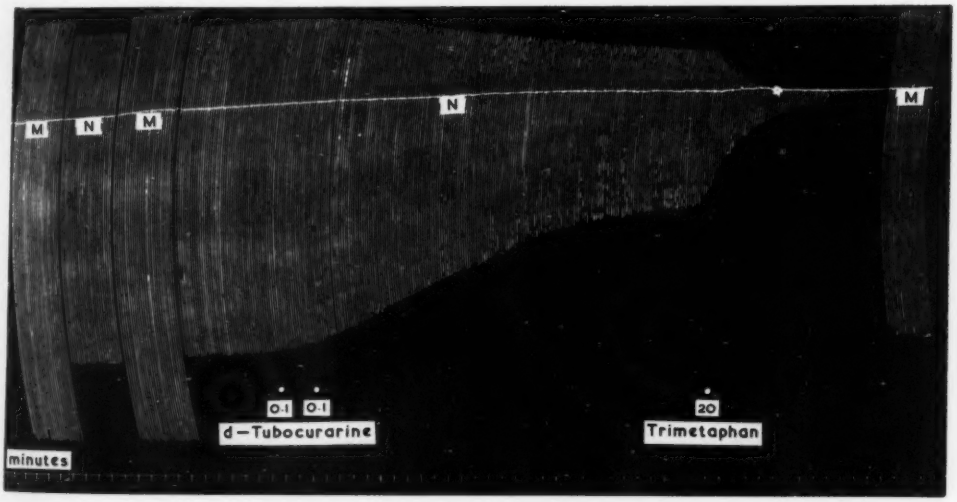


FIG. 5

Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation. N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.
Partial neuromuscular block produced by two 0.1 mg doses of d-tubocurarine. Complete block produced by a subsequent dose of 20 mg of trimetaphan.

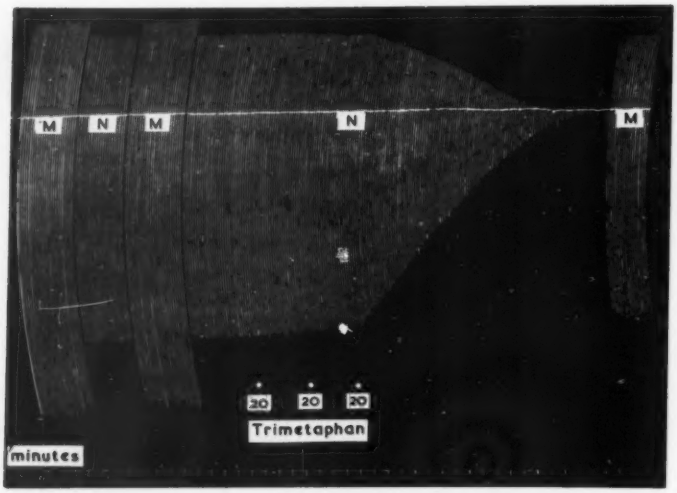


FIG. 6

Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation.
N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.
Same preparation as in figure 5 after washing and full recovery. Complete neuromuscular block after total of 60 mg of trimetaphan.

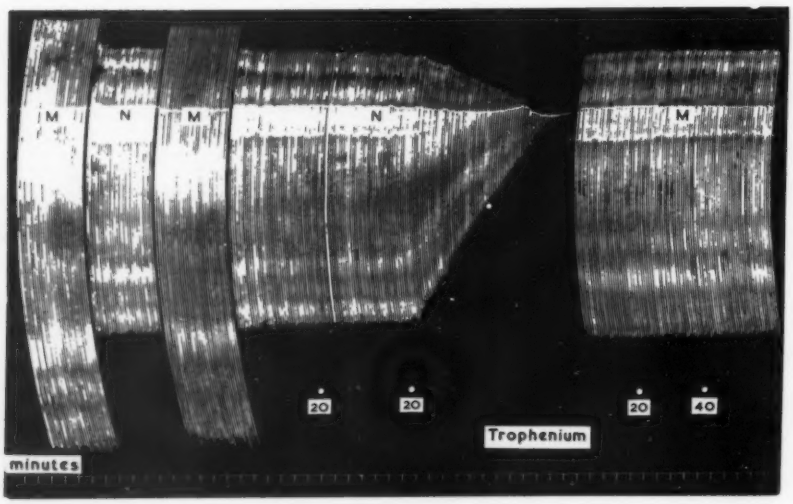


FIG. 7

Record of contractions of rat diaphragm preparation.
M = Direct muscle stimulation. N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.
Neuromuscular block produced by two 20 mg doses of homatropinium. Direct stimulation still produces an active response, unaffected by a further 20 mg and 40 mg of homatropinium.

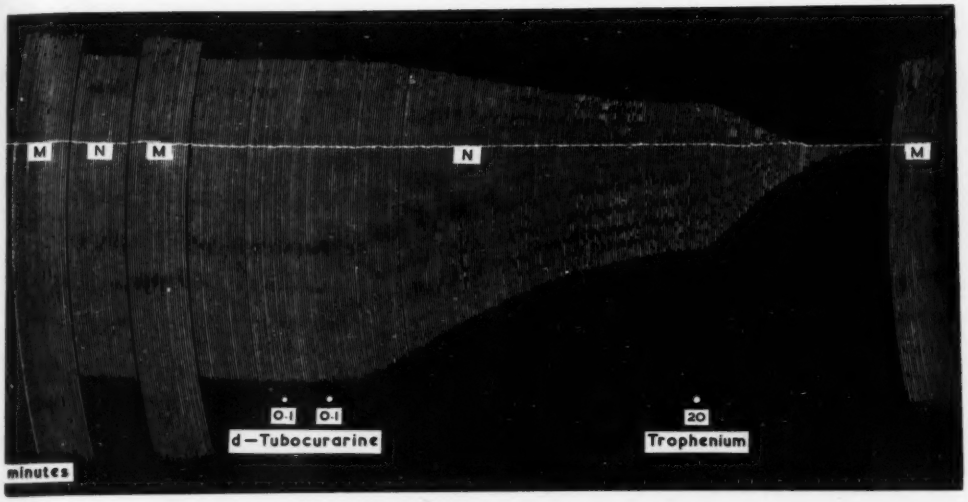


FIG. 8

Record of contractions of rat diaphragm preparation.

M = Direct muscle stimulation. N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.

Partial neuromuscular block produced by two 0.1 mg doses of d-tubocurarine. Complete block produced by a subsequent dose of 20 mg of homatropinium.

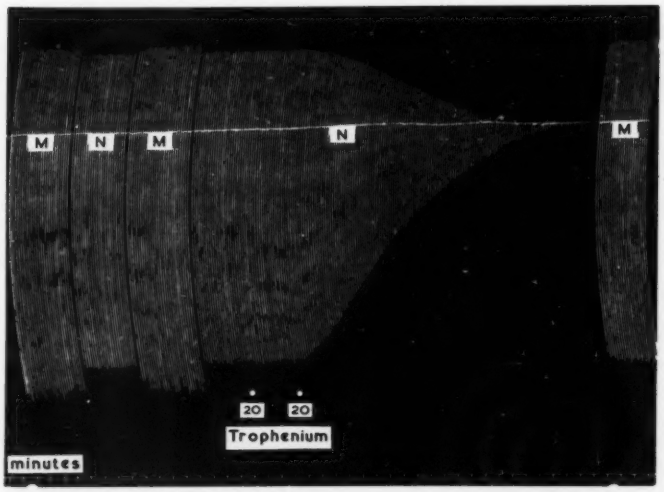
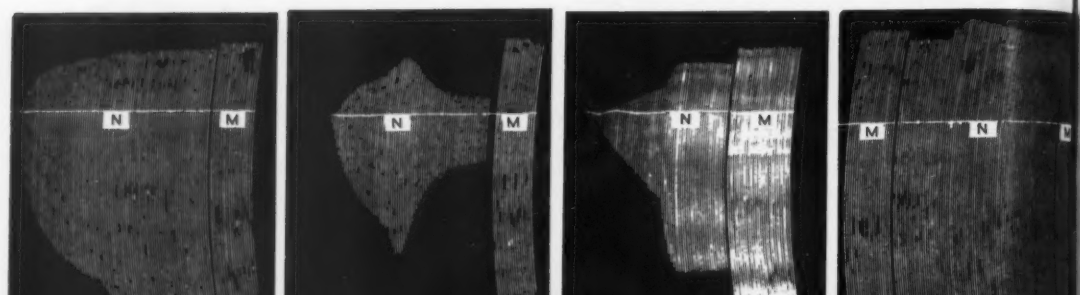


FIG. 9

Record of contractions of rat diaphragm preparation.

M = Direct muscle stimulation.
N = Indirect stimulation (via phrenic nerve).
All indicated doses in mg.

Same preparation as in figure 8 after washing and full recovery. Complete neuromuscular block after total of 40 mg of homatropinium.



(*a*) (*b*) (*c*) (*d*)

FIG. 10

Record of contractions of rat diaphragm preparation.

M = Direct muscle stimulation. N = Indirect stimulation (via phrenic nerve).

All indicated doses in mg.

(*a*) Preparation recovering from complete neuromuscular block produced by hexamethonium. Improvement in contractions following neostigmine 1 mg.

(*b*) Preparation recovering from complete neuromuscular block produced by trimetaphan. Decrease in amplitude of contractions following neostigmine 1 mg.

(*c*) Preparation recovering from complete neuromuscular block produced by homatropinium. Improvement in contractions following neostigmine 1 mg.

(*d*) Improvement in contractions following the addition of neostigmine 1 mg to preparation unaffected by other drugs.

In order to establish the effect of neostigmine alone, 1 mg was added to a fresh preparation. This produced an increase in the amplitude of the contractions, as shown in figure 10d.

DISCUSSION

All three ganglion blocking drugs examined were found capable of neuromuscular blockade. This has not previously been reported in the case of trimetaphan or homatropinium.

In no case was any initial muscle stimulation or fasciculation seen. This probably indicates that the neuromuscular blocking mechanisms are not of the depolarizing type. This is supported by the improvement in contractions that followed the addition of neostigmine to preparations recovering from total hexamethonium and homatropinium block. The neuromuscular blocking effect of hexamethonium, reported by Paton and Zaimis (1952), is recognized to be of nondepolarizing type. In the case of trimetaphan, however, the recovery from total block was halted, and, in fact, the block made more profound by the addition of neostigmine. Tewfik (1957) has shown experimentally that, in vitro, trimetaphan suppresses cholinesterase. It may be that this is the mechanism whereby trimetaphan upsets neuromuscular transmission, and this would explain the potentiation produced by neostigmine, which, of course, also has powerful anticholinesterase activity.

To assess their clinical significance, these results must be considered quantitatively.

In the case of hexamethonium, the huge total of 400 mg was required to produce neuromuscular block, in a perfusion bath of 200 ml capacity.

Even after partial curarization, 250 mg was required. It is unusual for more than 300 mg of hexamethonium bromide to be used in anaesthetic practice, and we consider, therefore, that, normally, the curare-like effect of this drug can be ignored. However, Payne (1957) has recommended caution in the administration of hexamethonium to patients receiving mecamylamine, as he considers that this combination might produce neuromuscular block.

Trimetaphan produced paralysis of the preparation after a total of 60 mg (30 mg per cent) had been given, but only 20 mg (10 mg per cent) was required after partial curarization. The clinical requirements of trimetaphan vary considerably. Large amounts may be needed in resistant patients, where tachyphylaxis occurs, when the position of the patient does not favour the production of hypotension, or if coarctation of the aorta exists. Vermeulen-Cranch (1956) records the use of 2,400 mg and doses of this order are not uncommon. In such cases we believe neuromuscular transmission may be depressed.

The fate of trimetaphan in the body is not known, but the transient hypotensive effect of a single dose suggests a rapid breakdown. Gertner et al. (1955) recovered, unchanged, from the urine only one third of the amount administered. If the remainder is, as Tewfik (1957) suggests, destroyed in vivo by pseudocholinesterase, then patients having a low pseudocholinesterase level would be more likely to show neuromuscular effects, particularly if relaxants or neostigmine are also given.

Homatropinium produced complete block in lower dosage than trimetaphan. After partial curarization only 20 mg (10 mg per cent) was required. In clinical use, Robertson (1957) reports the administration of 2,280 mg to one patient. It appears, therefore, that the neuromuscular blocking action of homatropinium may be of practical significance. A point in favour of this drug, as compared with trimetaphan, is that this curare-like effect is antagonized by neostigmine.

SUMMARY

Experiments to investigate the actions of hexamethonium, trimetaphan and homatropinium on neuromuscular transmission are described.

All three drugs are shown to produce neuromuscular block. Preliminary curarization reduces the dose required. Neostigmine antagonizes this action of hexamethonium and homatropinium, but potentiation occurs in the case of trimetaphan.

These results and their possible clinical implications are discussed.

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PRE-ANAESTHETIC MEDICATION WITH NEW DRUGS

A Comparative Study of the Clinical Effects of N-methylpiperidyl-3-methyl-phenthiazin, chlorpromazin, morphine-scopolamine, reserpine and placebo

BY

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THE search for the ideal pre-anaesthetic medication has been pursued for years and so far no drug or combination of drugs has been universally accepted. Recently a new group of drugs known as tranquilizers or ataraxic agents have been advocated for premedication; among the drugs used are N-methylpiperidyl-3-methylphenthiazin-(pecazine, Pacatal) (Horatz, 1954a; Sommer Pedersen, 1955a), chlorpromazine (Largactil) (Dobkin et al., 1956), and reserpine (Serpasil) (Taddei and Nasta, 1954).

The general purpose of premedication is to provide the patient with a comfortable dreamless sleep the night before the operation, and a pre-anaesthetic period with (1) sedation, (2) sleep and (3) amnesia. During anaesthesia and operation it is desirable to avoid secretions which may cause respiratory obstruction. Much has been written on the inhibition of autonomic reflex activity (e.g. Huguenard, 1953; Sommer Pedersen, 1955b) as one of the goals of premedication, but since no satisfactory means of estimating reflex activity exist, it will not be taken into consideration here. The almost classical belief that premedication lowers the metabolic rate is questionable. Haxholdt and Skov Jensen (1957) found no evidence in support of this theory when studying: pecazine, pecazine-allypropymal, pecazine-pethidine, chlorpromazine, morphine-scopolamine in comparison with placebo.

Morphine has been used as a pre-anaesthetic agent since it was first suggested by Lorenzo Bruno in 1850, but a disadvantage of morphine and related drugs is that these give maximal benefit to the patient only for a comparatively short period of time, and further that the interval between subcutaneous injection and induction of anaesthesia should be approximately $1\frac{1}{2}$ hours. The problems of timing and duration of action are negligible for the longer acting agents—pecazine, chlorpromazine and reserpine.

The present study is concerned with a clinical comparison of pecazine, pecazine + allypropymal (allylisopropylbarbituric acid), pecazine + pethidine, chlorpromazine, morphine + scopolamine, reserpine and placebo when used as agents for pre-anaesthetic medication. Its purpose was to obtain information of the relative efficacy of the drugs in question.

METHOD

The investigation was carried out on patients who were to undergo elective general or thoracic surgery. Cases for cardiac surgery, emergency cases, those in pain and in age groups below 7 years and above 85 years were excluded. All the patients receiving pecazine and some of the patients in pecazine-allypropymal and pecazine-pethidine groups were studied in one hospital, operated upon by one surgical team, while the remaining patients in the two last groups and from the other groups were studied in another hospital to which they were admitted for similar types of surgery and operated upon by a second surgical team. Otherwise the type of patients, anaesthesia and surgical interventions were similar.

All the patients were interviewed and observed three times: the day before operation, immediately before the operation, and the day after the operation. Only one person, the author, carried out these examinations. None of the patients knew that a test was being carried out, nor did they know the nature of the drugs used. Every

TABLE I

Comparability of groups.

Drug used	Total no. of patients	Sex		Age in years			Site of operation			Type of anaesthesia			
		Male	Female	Range	Mean ±S.E.	Median	Intra-thoracic	Intra-abdominal	Peri-pheral	Thiopentone, N_2O	Thiopentone, N_2O, relaxant	Thiopentone, N_2O, cyclopropane	Thiopentone, N_2O, ether
Pecazine	54	36	18	7–75	44 ± 2.3	44	21	17	16	1	44	1	8
Pecazine + Allypropymal	50	25	25	15–79	47 ± 2.3	47	15	20	15	3	41	1	5
Pecazine + Pethidine	54	33	21	7–85	50 ± 2.5	52	21	19	14	2	42	3	7
Chlorpromazine	60	27	33	13–75	47 ± 2.0	48	11	33	16	3	37	9	11
Morphine-Scopolamine	70	32	38	8–73	41 ± 2.2	39	8	41	21	5	48	10	7
Reserpine	50	25	25	15–69	42 ± 1.7	42	6	32	12	1	27	4	18
Placebo	51	28	23	17–67	44 ± 2.0	43	1	32	18	4	25	6	16

patient was told that the medication given was for the purpose of providing a good night's sleep and that the premedication the following morning would ensure a comfortable pre-anaesthetic period. This precaution was considered necessary so that the amount and nature of suggestion might be reasonably uniform for all patients.

A total of 389 patients divided into 7 groups were studied. The following dose schedules were employed:

(1) Pecazine: evening, 250 mg perorally; morning at 06.00 hours, 200 mg intramuscularly.

(2) Pecazine + pethidine: evening at 19.00, pecazine 50 mg p.o.; at 21.00, pecazine 50 mg i.m., pethidine 50 mg subc.; morning at 06.00, pecazine 50 mg i.m.

(3) Pecazine + allypropymal: evening at 19.00, pecazine 50 mg p.o.; at 21.00, pecazine 50 mg i.m., allypropymal 100 mg p.o.; morning at 06.00, pecazine 50 mg i.m.

(4) Chlorpromazine: evening, 50 mg p.o.; morning at 06.00, 50 mg i.m.

(5) Morphine + scopolamine: evening, allypropymal 200 mg p.o.; morning $1\frac{1}{2}$ hours pre-operatively, morphine 14 mg + scopolamine 0.6 mg subc.

(6) Reserpine: evening 2 mg p.o. (2 tablets); morning at 06.00, 2.5 mg i.m. (2 ml).

(7) Placebo: evening, 2 tablets p.o.; morning at 06.00, 2 ml i.m.

The doses indicated are the maximum doses for the male adult while the dosage for other categories was corrected according to sex, age and body weight. The choice of drug for any particular patient was randomly determined. The dosage of pecazine under (1) was chosen after an initial trial, which showed doses of 50–150 mg pecazine to be without any evidence of sedative effect. Under (2) pecazine is combined with pethidine, which combination is indicated by Horatz (1954a). The method of administration under (3) has been claimed to be a very satisfactory type of premedication (Sommer Pedersen, 1955a). Under (4) chlorpromazine is given in the doses generally accepted. Morphine-scopolamine, being one of the most commonly employed pre-anaesthetic medications, was used as standard. To obtain satisfactory effect of reserpine, the doses used under (6) were considerably higher than those used by other authors quoted.

The properties of the solution of chlorpromazine and pecazine necessitated the intramuscular route of administration. For practical reasons it was not possible to code all the various drugs to be tested. Only the two groups, reserpine and placebo, were tested with a "double blind" technique and coded.

The patients were interviewed for the second time the morning prior to the induction of anaesthesia, after the effect of the premedication had set in. They were questioned about the effect of the medication on the night's sleep, whether it was better, same or worse than usual, and as to the occurrence of dreams and unusual sleepiness the following morning. Further, the effects of the premedication were assessed by questioning about the degree of sedation, sleepiness, dryness of the mouth, postural dizziness, nausea, headache and pain in the region of injection. Objective evaluation consisted of observations on the state of sedation and sleepiness. During anaesthesia the incidence of annoying secretions was noted.

At the third visit to the patients, approximately 24 hours after the operation they were questioned as to the degree of amnesia for the last hour before the induction of anaesthesia, the incidence of nausea and vomiting, and severity of postoperative pain.

RESULTS

Comparability of groups: A total of 389 surgical patients were used for appraisal of the drugs listed. Table I shows the distribution of the patients in the various groups and the age and sex distribution. Apart from the pecazine group which shows divergence in the distribution of sex, it is apparent that with respect to sex the groups are comparable. The statistical analysis of the ages shows significant difference ($P<0.01$) between the eldest group (pecazine-pethidine) and the youngest (morphine-scopolamine), but as this variation is small, it was considered justified to compare the groups as to the effects of premedication. The types of operations and anaesthesia, however, showed too many differences and variable factors to permit comparison as to the incidence of postanaesthetic nausea, vomiting,

TABLE II

Comparison of sleep the night before operation with usual sleep; state after premedication before anaesthesia.

	Pecazine	Pecazine-Allypropymal	Pecazine-Pethidine	Chlorpromazine	Morphine-Scopolamine	Reserpine	Placebo
Total no. of patients	54	50	54	60	70	50	51
Comparison with usual sleep							
Better than usual	11 20%	17 34%	16 30%	15 25%	49 70%	4 8%	11 22%
Same	26 48%	28 56%	22 40%	22 37%	16 23%	15 30%	18 35%
Worse than usual	17 32%	5 10% (P<0.001)	16 30%	23 38%	5 7% (P<0.0005)	31 62%	22 43%
Dreams during night	2 4%	1 2%	5 10%	4 7%	4 6%	3 6%	4 8%
Unusual sleepiness the following morning	— —	14 28%	10 20%	6 10%	10 14%	6 12%	2 4%
Pre-anaesthetic state							
Sedation marked	3 6%	3 6%	2 4%	22 37%	57 82%	9 18%	10 20%
moderate	11 21%	15 30%	13 24%	10 16%	2 3%	4 8%	4 8%
none	40 73%	32 64%	39 72%	28 47% (P<0.025)	11 15% (P<0.0001)	37 74%	37 72%
Sleepiness marked	8 15%	1 2%	4 7%	14 23%	46 66%	7 14%	6 12%
moderate	7 13%	14 28%	9 17%	8 14%	5 7%	6 12%	6 12%
none	39 72%	35 70%	41 76%	38 63% (P<0.25)	18 27% (P<0.0005)	37 74%	39 76%

Level of significance: P=0.05

TABLE III

Memory of the immediate pre-anaesthetic period.

	Pecazine	Pecazine-Allypropymal	Pecazine-Pethidine	Chlorpromazine	Morphine-Scopolamine	Reserpine	Placebo
Total no. of patients	54	50	54	60	70	50	51
Amnesia for the immediate pre-anaesthetic period							
Total	0 0%	3 6%	4 7%	20 33%	57 81%	23 46%	16 32%
Partial	3 6%	6 12%	6 11%	14 21%	9 13%	8 16%	18 35%
None	51 94%	41 82%	44 82%	26 43% (P<0.0005)	4 6%	19 38% (P<0.075)	17 33%

Level of significance: P=0.05.

TABLE IV

Incidence of secretions during thiopentone–N_2O–relaxant anaesthesia.

	Pecazine	Pecazine-Allypropymal	Pecazine-Pethidine	Chlorpromazine	Morphine-Scopolamine	Reserpine	Placebo
Total no. of patients	54	50	54	60	70	50	51
No. of patients under thiopentone–N_2O–relaxant anaesthesia	44	41	43	37	48	27	24
Secretions	—	41 100%	41 95%	31 84%	0 0%	24 89%	24 100%

postoperative pain and number of analgesic injections required during the first 24 hours.

The *"sleep the night before operation"* as influenced by the various drugs is presented in table II. It will be noted that the patients in the morphine-scopolamine group had the most satisfactory sleep. The success rate in this group who received at night 200 mg of the barbiturate allypropymal is significantly higher than the rates of all other groups. The pecazine-allypropymal group who received 100 mg allypropymal the night before operation, merits second place, being significantly better than the placebo.

The incidence of dreams during the pre-operative night was found to vary between 2 and 10 per cent, while an unusual sleepiness the following morning varied from 4 per cent in the placebo group to 28 per cent in the pecazine-allypropymal group. Neither of these data have been subjected to statistical analysis.

Pre-anaesthetic sedation was obtained with the significantly highest rate by morphine-scopolamine and after this by chlorpromazine. Chlorpromazine was significantly better than a placebo. The all-over incidence of sedation obtained was 85 per cent for morphine-scopolamine, 53 per cent for chlorpromazine, 28 per cent for a placebo, and 26–36 per cent for the remaining groups.

Pre-anaesthetic sleepiness had an all-over incidence of 73 per cent in the morphine-scopolamine group while the variation in the other groups was from 24 per cent (placebo) to 37 per cent (chlorpromazine). Statistical analysis showed morphine-scopolamine to be significantly better than chlorpromazine, which latter was not being significantly better than a placebo.

Memory of the immediate pre-anaesthetic period. Table III shows the effect of the various drugs on the memory of the patients in the immediate pre-anaesthetic period. A total amnesia was obtained in 81 per cent of the patients in the morphine-scopolamine group, this result being significantly better than obtained by reserpine. In the reserpine group 46 per cent of the patients had total amnesia which was not significantly different from the rate of total amnesia obtained in the placebo group.

Secretions during anaesthesia were noted when being annoying and, to exclude the varying effects of different anaesthetics, only those patients were selected who had received thiopentone-N_2O-relaxant anaesthesia (table IV). In the lacumin group a high incidence of secretions was found, but the data was incomplete and this group was excluded. Only in the morphine-scopolamine group undesirable secretions were avoided, while all the remaining groups showed a high incidence of secretions, 84 to 100 per cent.

Side effects as occurring after the administration of the drugs before the onset of anaesthesia are listed in table V. The rash occurring in the reserpine group was a morbilliform flushing of the face and trunk of few hours duration. It disappeared spontaneously.

DISCUSSION

An attempt has been made to obtain a clinical appraisal of some tranquilizing drugs along the

TABLE V

Number of patients showing side effects.

	Pecazine	Pecazine-Allypropymal	Pecazine Pethidine	Chlorpro-mazine	Morphine-Scopolamine	Reserpine	Placebo
Total no. of patients	54	50	54	60	70	50	51
Dryness of mouth	47	41	31	35	58	22	15
Dizziness	2	3	0	14	15	6	2
Pain in region of injection	4	4	5	4	0	0	0
Headache	1	1	3	1	1	1	0
Nausea	0	0	0	0	1	1	0
Rash	0	0	0	0	0	4	0

lines suggested by Beecher (1952). Unfortunately practical reasons made it impossible to use the "double blind" technique in more than two of the seven groups studied. Otherwise randomization, concurrent comparison, use of a placebo, collection of data by only one investigator, and statistical analysis of data were employed.

The most satisfactory medication to provide a comfortable sleep the night before operation was allypropymal in a maximum dose of 200 mg (morphine-scopolamine group). It is interesting to note that the second best group was pecazine-allypropymal, receiving in the evening divided doses 50 mg each of pecazine supplemented by a maximum dose of 100 mg of allypropymal. The drugs in the remaining groups failed as hypnotic agents.

As to the data obtained on dreams during the night and unusual sleepiness the following morning, these reveal no relevant information; the incidence of dreams is considered lower than would be expected from that expected during normal sleep.

The subjective and objective data on sedation and sleepiness were pooled and not listed separately as did Lasagna (1954). As an example: when a patient on being questioned stated that he felt calm or tranquil and the objective evaluation revealed a nervous patient, "no sedation" would be recorded. Another example: a patient who stated he did not feel sleepy after the premedication yet despite this would fall asleep when left alone would be classified under "marked sleepiness".

The statistical analysis gave clear evidence of the effectiveness of morphine-scopolamine in providing satisfactory premedicative sedation. The second best drug was chlorpromazine; and all the other drugs failed. The finding that chlorpromazine is a mild sedative is in accordance with the reports of Dripps et al. (1955) and of Dyrberg and Johansen (1956). The latter, comparing chlorpromazine and morphine-atropine in a controlled study, found no significant difference in the sedation as obtained by these drugs.

Sleep was only provided with significantly different frequency by morphine-scopolamine, while none of the other drugs tested were effective in this respect.

To provide amnesia for the immediate pre-anaesthetic period morphine-scopolamine proved to be significantly better than any of the other drugs, which all failed in providing any satisfactory amnesia.

During thiopentone-N_2O-relaxant anaesthesia the great majority of patients in all groups except the morphine-scopolamine group, required repeated aspiration of the pharynx and trachea to keep the air passages clear of secretion. The course of anaesthesia as influenced by the drugs in other respects has been outside the scope of this investigation. It ought only to be mentioned that no serious complications occurred which could be ascribed to effects of the drugs tested.

Most patients experienced dryness of the mouth, but it was not clear as to whether this was related to nervousness or to a desirable antisialogogue effect of the drugs. Indeed, whether dryness of the mouth should be considered a side effect of premedication is open to discussion. Dizziness was most pronounced in the morphine-scopolamine and the chlorpromazine groups. As would be expected from the character of the solutions of the phenothiazine derivatives pain at the site of injection only occurred in these groups.

Nausea occurred in only one patient in each of the reserpine and morphine-scopolamine groups. This is interesting in respect of morphine-scopolamine, when it is considered that no patient was excluded, even if his history revealed poor tolerance to opiates. The occurrence of rash after reserpine has also been reported by Stephen et al. (1955).

This investigation shows that in the way used, reserpine fails to produce any of the desired effects—a conclusion which is contrary to the reports of Damia and Samele (1954), Migliavacca and Ferraris (1956), and Taddei and Nasta (1954), but in accordance with Stephen et al. (1955). The doses in this investigation were bigger but administered over a shorter period of time than those given by the authors quoted. The failure of pecazine alone or in combination with either allypropymal or pethidine to provide the effects stated as requirements of pre-anaesthetic medication must be reconciled with reports emphasizing its sedative and antisecretory effectiveness (Horatz, 1954b; Déchène, 1956; Williams, 1957; Davies, 1956; Sommer Pedersen, 1955a).

Beecher (1955) prefers barbiturate-atropine and condemns the use of morphine in pre-anaesthetic medications, unless a patient is having severe pain. However, he does not include amnesia amongst the goals at which to aim and does not mention scopolamine.

SUMMARY AND CONCLUSIONS

With the aims of pre-anaesthetic medication listed as comfortable sleep the night before operation, pre-anaesthetic sedation, sleep and amnesia, and antisecretory effect during anaesthesia, the incidence of these effects following six agents or combinations of agents (N-methylpiperidyl-3-methylphenthiazin alone or with allypropymal or pethidine, chlorpromazine, reserpine, and morphine-scopolamine) have been assessed in 389 surgical patients. The experimental design employed placebo control, concurrent comparison, randomization of subjects, statistical treatment of data, while the "double blind" technique was only carried out for placebo and reserpine.

The pre-operative night's sleep is best achieved by 200 mg allypropymal perorally. The most efficient pre-anaesthetic medication with only minimal side effects proved to be morphine (14 mg) with scopolamine (0.6 mg) subcutaneously, whereas chlorpromazine could only promote mild sedation. In the ways used neither N-methylpiperidyl-3-methylphenthiazin, alone or in combination with allypropymal or pethidine, nor reserpine were found to be of any value as premedicative agents.

ACKNOWLEDGMENTS

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LEVALLORPHAN IN ANAESTHESIA

BY

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ANALGESIC drugs used as supplements to nitrous oxide and oxygen have the great drawback that they depress respiratory rate and minute volume. A means of eliminating this would widen the scope of this otherwise most useful technique of anaesthesia.

Some years ago the drug nalorphine became available, and though Bodman (1953) drew attention to its power of reversing the respiratory depression due to pethidine employed as a supplement to nitrous oxide and oxygen, the idea was not followed up. More recently, as a result of the researches of Fromherz and Pellmont (1952) a drug analogous to nalorphine, levallorphan, has been developed. It was studied by Cullen and his associates (Cullen and Santos, 1954, 1955; Hamilton and Cullen, 1954; Gross and Hamilton, 1954) in relation to its antagonism to the parent drug levorphanol (Dromoran). It was also shown by them to have some antagonistic effect to the respiratory depression induced by pethidine and morphine. Its actions have also been studied by Eckenhoff and Funderburg (1954) and it has been used in anaesthesia with alphaprodine (Nisentil) by Stoetling and Hicks (1956) and by Foldes and his colleagues (1956a, b) (Swerdlow, 1957). The effects of levallorphan on pethidine given as a supplement to nitrous oxide and oxygen have not yet been studied in detail and it seemed worth while to investigate this.

METHODS

The action of levallorphan was studied in patients anaesthetized with nitrous oxide and oxygen during the quiet phases of an operation when stimulation from the surgeon's manipulations was unlikely to influence the rate or depth of respiration. Premedication, except where otherwise stated, was either with morphine 10 mg and atropine 0.65 mg, or with papaveretum 20 mg and hyoscine 0.2 mg. It was assumed that these doses were equi-analgesic. Anaesthesia was induced with sleep doses of barbiturate and where measurements of ventilation were carried out a cuffed endotracheal tube was employed. Suxamethonium was used to provide the necessary relaxation for intubation.

The effects of levallorphan were studied in two ways; first, by simple counting of the respiratory rate, and secondly, by following changes in the respiratory displacement.

Respiratory rates were counted for at least 10 consecutive respirations, or for 30 seconds. Where less than 10 respirations occurred in this period the average interval between the beginning of each successive inspiration was also measured and used as a check. The results were taken as correct to the nearest whole number and must in consequence have an error varying from 5 to 10 per cent.

Where respiratory displacement under anaesthesia was measured, a wet gas meter of a pattern similar to an ordinary domestic gas meter but with wider inlet and exit tubes was placed in the expiratory hose of a Coxeter-Mushin absorber (fig. 1).

A number of difficulties had to be circumvented before satisfactory results were obtained from this apparatus. It was found impossible to obtain accurate records unless only a basal oxygen flow was maintained. Any spillover flow passed through the meter on its way to the expiratory valve on the absorber head and superimposed a continuous flow on the intermittent respiratory displacement. It was also discovered that a period of some 30 seconds was required for the system to stabilize after a reduction in gas flow to basal levels before the recording needle moved regularly with each breath.

Further, this method involved closed circuit nitrous oxide and oxygen anaesthesia. It is notori-

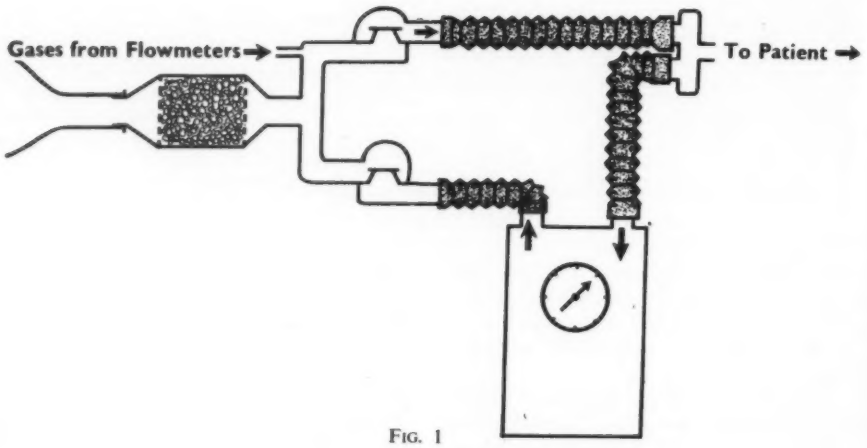

FIG. 1

ously difficult to maintain an even plane with this technique and in fact difficulties did arise when the period of measurement was prolonged. It was, however, possible to obtain consistent readings in all cases over at least 3, and often 4 minutes. Where readings were required over longer periods, intervals of at least 2 minutes of closed anaesthesia with a large spillover were interspersed (total flow 6 litres per minute of nitrous oxide and 2 litres of oxygen).

The inability to obtain records over long periods did not, however, vitiate the results because the most dramatic effects of pethidine and levallorphan on the respiratory displacement occur within a minute or so of their administration. (This observation has also been made by Foldes and his colleagues, 1956a.)

The method of measurement used could not have a high degree of accuracy as there was no guarantee that an exactly equal number of expirations would occur in each minute. In fact, the minute volume figures quoted may have an error of as much as half a litre. This is, however, small compared with the changes produced by effective doses of levallorphan in profound respiratory depression from analgesic drugs and is not sufficient to make the results valueless.

RESULTS

The classical indication of the respiratory effects of analgesic drugs is the slowing of the breathing which follows their administration. This criterion was employed in the study of the modifying action of levallorphan on pethidine. This latter drug was given in incremental doses of 25 to 50 mg to 18 patients in quantity sufficient to slow breathing sharply. As soon as this effect was apparent 0.5 mg levallorphan was injected intravenously. The respiratory rate in every case showed a prompt improvement within a minute (fig. 2) and the maximum recovery was usually present within 3 minutes. The maximum rate in this period is set out for all the cases in table I.

Bradypnoea due to 25 mg was more than reversed and as a number of the patients already had some slowing of the breathing from previous doses of pethidine, the final respiratory rate was higher than the initial. Respiratory depression due to 50 or more milligrammes of pethidine was not wholly undone by 0.5 mg levallorphan. In two cases, where some 35 mg of pethidine was followed by 0.5 mg levallorphan, the initial and final respiratory rates were the same.

In another series of 18 patients an attempt was made to prevent respiratory depression by giving levallorphan before pethidine. In these cases 0.5 mg of levallorphan was injected intravenously and followed by 25 or 50 mg pethidine. Both doses produced some slowing of the breathing (table II). The initial dose of levallorphan did not affect the respiratory rate.

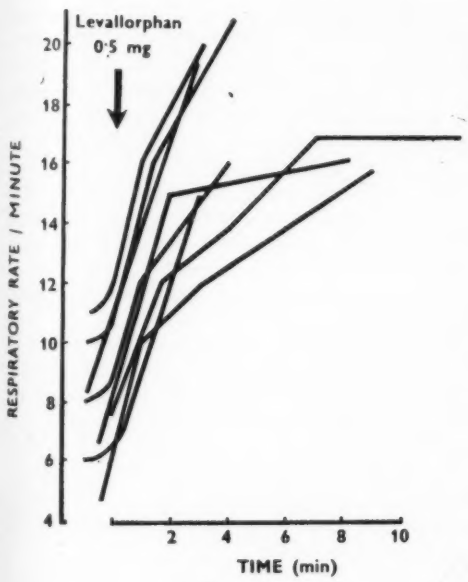

FIG. 2

Respiratory rate changes after levallorphan in patients depressed by pethidine.

Premixed solutions of pethidine and levallorphan were also tested. Initially the drugs were given in the 200:1 ratio suggested by Cullen and his co-workers (1955). Subsequently 100:1 and 50:1 mixtures were given. The respiratory rates were counted before and after the administration of the drug mixture. The second figure quoted is the minimum level attained in the first 3 minutes after the injection. In no case was complete protection from respiratory slowing obtained, but there was a very definite reduction in the percentage fall in respiratory rate with each increase in the amount of levallorphan in the mixture (table III). A statistical study of these results by the method of Analysis of Variance is appended to this article.

Respiratory Displacement.

It was realized that studies of respiratory displacement would give a better indication of the changes in respiratory function produced by pethidine and levallorphan. As has been indicated in the section on methods, however, these proved difficult to carry out. It was, however, possible to show that the administration of levallorphan in doses of as little as 0.25 mg would improve

TABLE I
(Based on multiple observations on 18 patients)

	Cases	Respiratory rate		
		Before pethidine	After pethidine	After levallorphan 0.5 mg
Pethidine 25 mg	12	14.5±3.2	7.1±1.8	16.0±2.2
Pethidine 35 mg	2	15 (14–16)	6 (5–7)	15
Pethidine 50 mg	8	18.0±1.4	5.4±5.3	15.8±1.4
Pethidine 65 mg	1	20	5	15
Pethidine 75 mg	2	20	8.5 (7–10)	13 (12–14)
Pethidine 100 mg	2	25 (24–26)	10	15 (14–16)

TABLE II

Drugs given	Cases	Respiratory rate per min		Fall in respiratory rate	Percentage fall in respiratory rate
		Before	After		
Levallorphan 0.5 mg	10	19.4±3.2	19.3±3.7	0.1±1.6	0.5
Levallorphan 0.5 mg followed by pethidine 25 mg	16	20.4±5.7	17.8±4.8	2.6±3.3	13
Levallorphan 0.5 mg followed by pethidine 50 mg	10	21.8±6.7	17.5±6.9	4.3±2.2	20

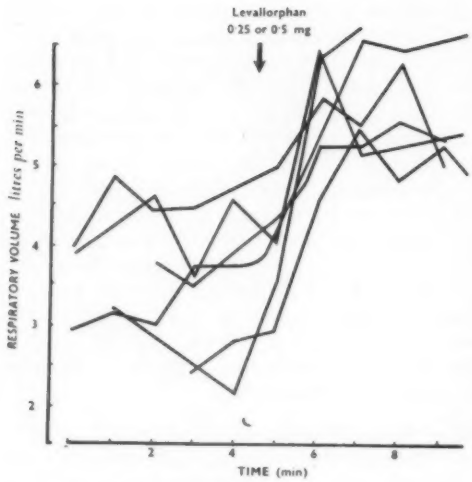

FIG. 3
Changes in respiratory minute volume after levallorphan in patients depressed by pethidine.

respiratory depression due to pethidine in patients under anaesthesia. The actual changes which occurred are given in table IV. The time course of events in so far as it was followed is in figure 3. It was possible to follow 4 of these patients at intervals for periods of up to 1 hour after the levallorphan had been given. There was no tendency to relapse into depression during this period. Indeed, once the minute volume had been restabilized it remained remarkably steady during quiet phases of the operation.

The changes in tidal volume were inconstant by comparison with the changes in rate and minute volume (fig. 4). Further, even when an increase in tidal volume did occur it was accompanied by a change in respiratory rate. It therefore seems as if the use of the respiratory rate alone as a measure of respiratory depression in these cases was justified, though it is obviously not right to assume that there is a simple arithmetical relationship between minute volume and rate of breathing.

TABLE III

Drugs given	Cases	Respiratory rate		Fall in respiratory rate	Percentage fall in respiratory rate
		Before	After		
Pethidine 25 mg	14	23.0±6.5	16.1±4.81	6.9±2.1	30
Pethidine 25 mg, levallorphan 0.125 mg	13	21.4±4.9	16.1±4.8	5.3±2.1	25
Pethidine 25 mg, levallorphan 0.5 mg	16	20.2±6.0	16.7±5.7	3.5±5.6	17
Pethidine 50 mg	9	25.1±5.8	12.8±2.7	12.3±2.1	49
Pethidine 50 mg, levallorphan 0.25 mg	8	22.1±5.7	14.8±3.4	7.3±3.6	33
Pethidine 50 mg, levallorphan 0.5 mg	5	26.2±5.1	19.0±5.1	7.2±4.6	27

TABLE IV
The effect of levallorphan on the respiration of patients with depression due to pethidine.

Case No.		7	14	14	16	16	27	30	31	36
Dose of levallorphan (mg)		0.25	0.25	0.25*	0.25	0.25*	0.25	0.25	0.5	0.5
Minute volume, l./min	before	8.0	4.2	5.4	4.2	4.8	2.7	3.2	3.0	3.4
	after	9.1	5.8	6.0	5.3	5.2	5.1	6.1	6.5	5.3
Respiratory rate, per minute	before	—	14	17	14	18	10	8	12	11
	after	—	14	18	20	20	13	14	20	16
Tidal volume, ml	before	—	300	320	300	270	270	400	250	310
	after	—	420	331	270	260	390	440	330	330

* Second dose in same patient.

TABLE V

The effect of levallorphan on respiratory depression due to morphine (papaveretum-hyoscine) and dipipanone.

Case No.	Cause of respiratory depression	Mean ventilation l./min		Dose of levallorphan (mg)	Respiratory rate per min		Tidal volume ml	
		Before	After		Before	After	Before	After
11	Morphine	3.7	8.2	0.25	16	18	230	460
11*	Morphine	4.2	5.2	0.25	18	22	230	240
23	Dipipanone 379 C 48	1.7	5.1	0.25	9	10	190	38

* Second dose in same patient.

Antagonism to other Analgesic Drugs.

Levallorphan removed some of the respiratory depression, as measured by the minute volume, due to papaveretum (Omnopon) and dipipanone (379 C 48) in the human subject (table V). Improvement in respiratory rate in 4 patients depressed by heroin was also demonstrated. There was by no means a restoration to normal levels in these cases, but such recovery as took place was maintained and there was no tendency to relapse into depression during the succeeding 4 hours.

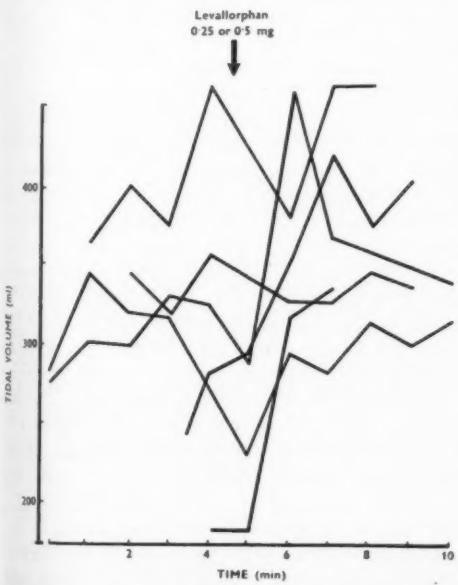

FIG. 4

Changes in tidal volume after levallorphan in patients depressed by pethidine.

The Effect on Analgesia.

As Cullen and Hamilton (1955) had suggested that a 200 to 1 mixture of pethidine and levallorphan would produce analgesia without respiratory depression, these drugs were administered in that ratio to anaesthetized patients according to the normal indications for the use of analgesic drugs as supplements to nitrous oxide and oxygen. In a control group of 34 patients a mean amount of 51 mg of pethidine alone was required to produce the analgesia needed for the making of the initial skin incision. In 24 comparable cases anaesthetized by identical techniques 58 mg of pethidine combined with 1/200th of this amount of levallorphan was required to produce analgesia. The difference is not statistically significant, nor would it be expected to be as the pethidine was given in increments of 25 mg. It would therefore seem that in the 200:1 ratio there is little less analgesia from the simultaneous administration of levallorphan with pethidine.

DISCUSSION

This investigation has shown that levallorphan, like nalorphine, is an effective antagonist in man to a large number of analgesic drugs of the morphine group. This point serves to emphasize the fact that all these agents are effective at common receptors, and it seems probable that the active chemical group which fits these structures is something relatively simple. The main mass of the molecule serves merely to orientate it so that the active group fits in.

The second point of interest is the fact that with pethidine at least, the antagonistic effect of levallorphan was not at its best when it was given simultaneously with the analgesic drug. Perhaps its seemingly greater effectiveness afterwards is to be related to the fact that carbon dioxide accumulation due to respiratory depression was present when it was thus given. There was, however, little evidence of a temporary hyperpnoea on the recovery by the respiratory centre of its sensitivity to carbon dioxide with return to a more depressed level as the carbon dioxide was blown off. The limitations of the method of estimation may have made it impossible to obtain full evidence on this point.

It is, however, interesting that Stoetling and Hicks (1956) comment that levallorphan given with alphaprodine is apparently less effective as an antagonist than is levallorphan given subsequently to alphaprodine in the manner described by Foldes and his colleagues (1956a, b). The same conclusion was reached by Gross and Hamilton (1954) concerning levorphanol and levallorphan mixtures given in the same syringe and given separately.

This investigation has unfortunately not wholly proved the thesis that levallorphan reverses respiratory depression without at the same time removing analgesia. With the 1:200 ratio little extra analgesic was required to produce satisfactory operating conditions. Quite considerable respiratory depression also occurred in some cases, but it was undoubtedly less than in the controls. Herxheimer and Sanger (1957) and Roberts and her co-workers (1957) have, however, both indicated that in the 1:200 ratio levallorphan-pethidine mixtures produce little respiratory depression in patients to whom no other analgesic drugs have been given, and it is probable that the difference in the response of the cases of this series is traceable to the effect of premedication and has no scientific meaning.

The Clinical Use of Levallorphan.

It is doubtful to what extent levallorphan will find a place in clinical anaesthesia. Nalorphine was shown by Bodman (1953) to be an effective antagonist to respiratory depression produced by pethidine. It has not in fact found wide application and there is no reason to suppose that levallorphan will prove any more popular unless it appears from extended trial to have less vasomotor and emetic action than the former drug. The immediate conclusion seems to be that levallorphan is a drug which can usefully be employed if the administration of an analgesic drug to an anaesthetized patient produces unexpectedly profound respiratory depression.

The use of pethidine-levallorphan mixture, or the prophylactic administration of levallorphan to prevent depression of respiration by analgesic drugs, is of more doubtful value in anaesthesia. Where the antagonist is given in the 200:1 ratio some respiratory depression regularly occurs, though the severity of it is diminished. In the anaesthetized patient, however, the respiratory rate is a valuable guide to the degree of analgesia which is present when pethidine is being used to supplement nitrous oxide and oxygen. Indeed, the drug can very satisfactorily be given in quantity sufficient to keep the respiratory rate between 12 and 16/min. If prophylactic levallorphan is employed to minimize this respiratory depression the indications for the administration of extra analgesic may be blurred.

The studies here reported have not included any investigations of the use of levallorphan in obstetrics. However, in view of the fact that 0.5 mg of levallorphan produced satisfactory reversal of respiratory depression induced by analgesic drugs in the adult under anaesthesia it would seem reasonable to conclude that a mother at term might satisfactorily be given pethidine in relatively unlimited quantity during her labour and be anaesthetized with nitrous oxide, oxygen, and a pethidine supplement, for delivery when necessary, provided that an effective dose of levallorphan is injected some 10-15 minutes before the child is born. By this time the antidote should have reversed not merely the maternal but also the foetal respiratory depression. The use of premixed doses of pethidine and levallorphan in labour has been investigated in great detail by Roberts and others (1957).

SUMMARY

Levallorphan has been used as an antidote to respiratory depression in man. It was shown with the aid of minute volume studies that respiratory depression due to pethidine, morphine, and

dipipanone was reversed by levallorphan; reversal of respiratory depression due to heroin was shown by change in respiratory rate. This criterion was used to extend the work with pethidine. Using this criterion it was shown that levallorphan in a ratio approximating to 1:70 would largely eliminate respiratory depression due to pethidine previously given to patients anaesthetized with nitrous oxide-oxygen after opiate premedication and barbiturate induction.

STATISTICAL STUDY

The results of the study in tables I, II, and III were analyzed in two ways, using the technique of Analysis of Variance.

(1) The respiratory rate after each injection was compared with the rate before in the same patient, and from this the effect of the injection on the respiratory rate for each group was assessed. It was thus possible to demonstrate whether the injection of the drugs had produced a significant change in the breathing. Using this method of study the following data were obtained.

Pethidine 25 mg, significant fall	$P<0.01$
Pethidine 25 mg, levallorphan 0.125 mg, significant fall	$P<0.01$
Pethidine 25 mg, levallorphan 0.5 mg, significant fall	$P\ 0.02>0.01$
Pethidine 25 mg, following levallorphan 0.5 mg, significant fall	$P\ 0.02>0.01$
Pethidine 50 mg, significant fall	$P<0.01$
Pethidine 50 mg, levallorphan 0.25 mg, premixed, significant fall	$P<0.01$
Pethidine 50 mg, levallorphan 0.5 mg, premixed, significant fall	$P\ 0.02>0.01$
Pethidine 50 mg, following levallorphan 0.5 mg, significant fall	$P\ 0.05>0.02$

(2) The change in rate was also studied and an analysis made of the fall in respiratory rate produced by groups of injections. By this means it was possible to demonstrate the significance of differences in the fall in respiratory rate in two groups. Using this method the following results were obtained.

Difference between fall produced by:		
Pethidine 25 mg, levallorphan 0.125 mg, and pethidine 25 mg		$P>0.05$
Pethidine 25 mg, levallorphan 0.5 mg, and pethidine 25 mg		$P<0.01$
Pethidine 25 mg, after levallorphan 0.5 mg and pethidine 25 mg		$P<0.01$
Pethidine 25 mg, after levallorphan 0.5 mg, and pethidine 25 mg, levallorphan 0.5 mg, premixed	NS	$P>0.05$
Pethidine 50 mg, levallorphan 0.25 mg, and pethidine 50 mg		$P\ 0.02>0.01$
Pethidine 50 mg, levallorphan 0.5 mg, and pethidine 50 mg		$P\ 0.05>0.02$
Pethidine 50 mg, after levallorphan 0.5 mg, and pethidine 50 mg		$P<0.01$
Pethidine 50 mg, after levallorphan 0.5 mg and pethidine 50 mg, levallorphan 0.5 mg, premixed	NS	$P>0.05$

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DECAMETHONIUM IODIDE: A REAPPRAISAL

BY

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DECAMETHONIUM iodide (C.10) was first described by Barlow and Ing, and by Paton and Zaimis, in 1948. The following year it was introduced into anaesthesia as a result of the work of Organe, and of Hewer, Lucas, Prescott and Rowbotham.

Apart from the initial enthusiasm decamethonium has never found much favour with anaesthetists. In 1950 an editorial in the *Lancet*, comparing it with Gallamine, stated that the position of decamethonium was "less happy, mainly because no satisfactory antidote for it had yet been found". It went on to mention reports of delayed recovery and to conclude that "much more experience will be needed before its place in anaesthesia can be fully assessed".

The position has changed little since. Two years later the same journal stated in an annotation that "of the depolarizing group decamethonium had a brief period of popularity", and again the reason given for its failure to replace other relaxants was lack of a suitable antidote. Then in 1954, describing the Cardiff anaesthetic record system, Mushin, Lewis-Faning and Morgan wrote, "decamethonium, though commonly used at the time our card was first designed, is now little used and has been deleted from the record in the latest edition"; and Lee (1953), in his *Synopsis of Anaesthesia*, remarks that he seldom feels the need of this relaxant. It is hardly surprising that Burroughs Wellcome & Co. are ceasing to market their preparation, Syncurine (personal communication).

CRITICISM OF DECAMETHONIUM

It is interesting to consider the reasons for the fall from grace of decamethonium. The principal one is that it has no suitable antidote, a shortcoming which was aggravated by the almost simultaneous introduction of gallamine (Mushin, Wien, Mason and Langston, 1949), a drug effectively antagonized by neostigmine. It will be recalled that hexamethonium and pentamethonium bromide were at one time considered as possible antidotes to decamethonium but proved to be unreliable and indeed, owing to their hypotensive dangerous action.

The employment of decamethonium in anaesthesia was further discouraged by reports of persistent intercostal paralysis (Gray, 1950; Harris and Dripps, 1950; Hunter, 1950; Vetter and Nicholson, 1950; Barry, Straton and Sutherland, 1951; Guerrier and Mason, 1952), and of cardiovascular effects, viz., tachycardia, bradycardia and hypotension (Hunter, 1950; Guerrier and Mason, 1952) following the use of the drug. Finally, there were some who regarded its sharp end-point as an embarrassment to the smooth conduct of anaesthesia.

It is my opinion that a disproportionate amount of attention has been paid to the possible disadvantages of decamethonium. This view is supported by my own experience and that of my colleagues in the Dundee Teaching Hospitals who have used the drug extensively over the years. In proper dosage it has been found to be a reliable relaxant with no apparent side-effects, and to have a unique and valuable place in clinical anaesthesia.

The criticisms which have been levelled against decamethonium are not difficult to answer. The fact that it has no antidote is a poor objection to its employment in anaesthesia; to state that it does not need one is to present a more accurate picture of the situation. It is the only relaxant of reasonable duration of action which, even after full paralyzing doses, possesses this advantage. The sharp end-point, far from being an embarrassment, constitutes the most attractive

characteristic of decamethonium in anaesthesia. The complication of persistent intercostal paralysis is completely avoidable if dosage is not excessive. We have encountered no evidence of cardiovascular effects, and it is my firm opinion that they must be rare and of no practical significance.

SOME PHARMACOLOGICAL CONSIDERATIONS

The chemistry and pharmacology of decamethonium iodide have been thoroughly described (Paton and Zaimis, 1949; Burns and Paton, 1951; Paton, 1952; Foldes, 1954; Hunter, 1954; Paton, 1956; Burn, 1957). It is, however, relevant to mention certain characteristics of importance to its clinical use.

Injected intravenously, decamethonium iodide reaches its maximum effect in about 5 minutes. In a lightly premedicated adult of average build, following an induction dose of up to 750 mg, 5 mg decamethonium produces apnoea of approximately 20 minutes duration, provided slight hyperventilation with nitrous oxide/oxygen through a soda lime absorber is maintained. Within 5 minutes of the start of diaphragmatic contractions the effects of the drug have generally disappeared.

Although decamethonium is a depolarizing type of relaxant, the occurrence of obvious muscle fasciculations following induction with the normal dose of thiopentone is unusual. However, I have frequently succeeded in demonstrating them by giving a full dose of decamethonium (5 mg) immediately after a small amount of thiopentone (150 mg). The conscious person feels these as cramps (Organe, Paton and Zaimis, 1949; Hewer, Lucas, Prescott and Rowbotham, 1949), and the administration of a "test dose" of 1 mg was described by Gray (1950) as unpleasant for the patient. For this reason it is inadvisable to inject decamethonium before inducing sleep. The incidence of fasciculation seems to be related to the blood-level of adrenaline (Paton and Zaimis, 1950). Postoperative muscle pain does not appear to follow the use of decamethonium.

Decamethonium and Neostigmine.

Decamethonium (like suxamethonium) iodine is a relaxant of the depolarizing type, its effect being potentiated by the anticholinesterases. Therefore neostigmine must not normally be used in an attempt to reverse its action. However, in 1952, following experiments on animals, Zaimis reported that decamethonium and suxamethonium could no longer be described as purely depolarizing, and postulated the development in certain circumstances of a "dual block", first of all depolarizing and later changing to a competitive type reversible by anticholinesterases. At the same time Churchill-Davidson and Richardson (1952) drew attention to the fact that in myasthenic patients the affinity of the motor endplate for decamethonium changes and a block characteristic of competitive inhibition occurs, reversible by neostigmine. Subsequent to numerous clinical reports of neostigmine (or edrophonium—Bullough, 1957) effectively dispelling "prolonged apnoea" following suxamethonium (Grant, 1952; Ruddell, 1952; Hodges, 1953; Cowan, 1954; Argent, Dinnick and Hobbiger, 1955; Hodges, 1955; Brennan, 1956; Paletz, 1956; Bullough, 1957; Jowell and Wood-Smith, 1957), it seems reasonable to accept that the depolarizing relaxants sometimes produce a block reversible by anticholinesterases, particularly if given in large doses. Of especial interest is Ruddell's patient in whom a paralysis caused by heavy dosage of decamethonium (13 mg) and suxamethonium (250 mg) was dramatically reversed by neostigmine (6 mg).

Case Reports.

The following is a report of two similar examples.

The first concerns an elderly man undergoing hemicolectomy to whom I illadvisedly gave a total of 12.5 mg decamethonium over a period of 90 minutes. At the end of the operation his general condition was good but his respirations were only diaphragmatic and they remained so for half an hour. Neostigmine 2 mg was then cautiously injected intravenously with the result that normal breathing was restored immediately.

The second case is better documented and is given in detail.

The patient was a healthy woman aged 35 years for ureterolithotomy, an operation expected to last about 45 minutes; in fact, it occupied over 2 hours.

Premedication was pethidine 100 mg and atropine 0.6 mg. Anaesthesia was induced by thiopentone 500 mg and decamethonium 7.5 mg. The patient was intubated and respiration controlled with a 2:1 mixture of nitrous oxide and oxygen through a circle absorber. The operation was being done through a paramedian incision and 45 minutes later the surgeon complained of "tightness", and, as the end was not in sight, the anaesthetist gave a further 5 mg of relaxant, making

the total dose of decamethonium 12.5 mg. Approximately 75 minutes after induction (half an hour after the second dose of C.10) the patient began to breathe spontaneously but inadequately, and anaesthesia was continued with cyclopropane and oxygen, and assisted respiration. For the final 15 minutes the patient breathed only oxygen. At the end of the operation her condition was good, but her respirations remained completely diaphragmatic, with marked "chin tug", and this state persisted for the next quarter-hour. The anaesthetist then felt that neostigmine might be worth trying but he was naturally diffident about giving it and decided to wait a little as "she was bound to breathe properly soon". However, 10 minutes later there was no improvement and 2.5 mg of neostigmine was injected slowly intravenously. Almost immediately there was an obvious change in respiration in that inspiration, instead of being a sudden jerk, became drawn-out and deeper. Within 3 or 4 minutes breathing was normal and the patient's reflexes had returned.

It cannot be emphasized too strongly that the fact that neostigmine can sometimes reverse decamethonium should be of little more than academic interest. The above report concerns cases of frank overdosage which need never occur; in such instances the administration of the short-acting anticholinesterase edrophonium and observation of its effect before giving neostigmine would appear to be a better procedure.

CLINICAL CONSIDERATIONS

Advantages of Sharp End-Point.

From the point of view of the practising anaesthetist the outstanding characteristic of decamethonium iodide is that it is the only relaxant available which will produce total relaxation of about 20 minutes duration, and, within 5 minutes or so of beginning to wear off, have left no trace of its effect. This abrupt wearing-off, far from being an embarrassment, is a real advantage. The only jarring note in modern relaxant techniques with tubocurarine or gallamine is that they frequently depend on the use of neostigmine, with its undesirable side-effects. The employment of decamethonium in suitable cases can reduce considerably our dependence on this drug; the rapid, complete recovery without neostigmine of a patient who, following a single injection of relaxant, has been totally paralyzed for a reasonable time puts the finishing touches to an anaesthetic pattern of undoubted usefulness. It may also be noted that patients who have been spared neostigmine seem to be less restless in the immediate postoperative period. Anyone who has experienced the intense colic and general wretchedness which follows the intravenous injection of 2.5 mg (preceded by atropine 0.6 mg) will agree that there may be something in this observation.

Dosage of Decamethonium.

The usual dose of decamethonium iodide is 5 mg, and this is not often exceeded. Hunter's advice, given in 1950, that 10 mg should be regarded as the absolute maximum, still holds good. Allowance must be made for the general condition and age of the patient; children are relatively resistant, and, as is to be expected (Rees, 1954; Stead, 1955), infants appear to show a resistance to this depolarizing relaxant.

If the above rule is followed and overdosage avoided, no side-effects will be encountered; there will be no persistent intercostal paralysis and no worries from cardiovascular disturbances. In our experience there have been no cases of prolonged apnoea.

Should the initial dose wear off prematurely, in a fit subject it may be repeated up to a total of 10 mg where the end of the operation is not in sight, but generally it is better to continue with an inhalational agent such as cyclopropane, or with suxamethonium. The introduction of cyclopropane, even in the unintubated, can usually be accomplished smoothly, but there is no doubt that the advent of suxamethonium has given us more confidence in dealing with this situation. Decamethonium is clearly not the relaxant of choice for operations likely to last longer than 30 to 45 minutes and it sometimes happens that one is caught out, e.g., the closure of a perforation develops into a partial gastrectomy. In this event it is best to proceed as outlined above.

Occasionally a patient is still apnoeic at the end of operation. If the technique outlined above has been followed this is never more than a minor inconvenience lasting only a few minutes. It is as well to remember that the relaxant drugs are not infrequently blamed for this state when attention to other possible causes, e.g., an excess of premedication or anaesthetic, or inadequate resuscitation of an ill case, would be of more value.

Indications for Decamethonium.

Decamethonium iodine has a definite place in anaesthesia for many operations of medium duration. It is not suitable for either very brief or prolonged procedures. Even in cases where

full relaxation is not required it can be a useful drug, facilitating the administration of the lightest possible anaesthetic combined with perfect operating conditions and consequently the minimum after-effects.

The claims of decamethonium are enhanced when it is particularly desired to avoid the use of neostigmine, e.g., in patients suffering from asthma or bronchitis, and in those with cardiac disease.

Decamethonium is not entirely suitable for intubation. Even 2 or 3 minutes after injection the jaw may still retain tone and it sometimes exhibits clonus (Doughty, 1950). Suxamethonium surmounts this difficulty; although the mixing of drugs is criticized by some, it must be said that suxamethonium together with decamethonium in a syringe forms a most effective combination.

It is impossible to present a clear-cut list of operations in which the use of decamethonium is especially suitable. Examples are appendicectomy, closure of a perforated peptic ulcer, herniorrhaphy (simple and strangulated), cystoscopy and some prostatectomies. Decamethonium is also of value in bronchography under general anaesthesia by virtue of its profound relaxant effect and sharp end-point without recourse to neostigmine.

Illustrative Cases.

The typical use of decamethonium in anaesthesia is illustrated as follows:

The patient was a healthy man aged 23 years.

Premedication was pethidine 100 mg and atropine 0.6 mg. Anaesthesia was induced by thiopentone 500 mg, followed by decamethonium 5 mg, and respiration was controlled with a 2:1 mixture of nitrous oxide and oxygen.

Twenty minutes later, just before closure, diaphragmatic respirations were beginning. A 50 per cent mixture of cyclopropane and oxygen was introduced until the peritoneum was closed, the remainder of the operation being covered by nitrous oxide and oxygen. At the end the patient was opening his eyes and in full command of his reflexes.

An alternative to cyclopropane would have been the injection of a small amount of suxamethonium.

Decamethonium iodide is, in my opinion, the preferable relaxant for Caesarean section. The following is a description of the technique employed:

Premedication is with atropine only.

For a few minutes before induction the patient is encouraged to breathe a 2:1 mixture of nitrous oxide and oxygen. Thiopentone 150 mg is rapidly injected, followed by a mixture of decamethonium 5 mg and suxamethonium 50 mg. A cuffed endotracheal tube is at once introduced and respiration controlled with nitrous oxide (4 l.) and oxygen (2 l.) with the absorber off, in order to spare the infant the effects of hyperventilation. When the baby has been delivered (a procedure which may be performed at leisure) the mother is generally beginning to breathe and the anaesthetic is continued in the usual manner with cyclopropane.

With the minimum basal sedation normally used in these cases it is of importance to give nitrous oxide in a concentration over 50 per cent.

On the other hand, if the patient has for any reason been appreciably sedated pre-operatively, thiopentone should be avoided and induction carried out by means of nitrous oxide and oxygen, with a little cyclopropane where necessary.

Decamethonium may be injected intramuscularly with hyaluronidase in infant anaesthesia and has the advantage over suxamethonium of providing a longer period of relaxation. The same sharp end-point is observed. Its use in infants is illustrated as follows:

The first case was a baby of 8 lb. 12 oz. (4 kg) for a Ramstedt operation.

After premedication with atropine 0.3 mg, anaesthesia was induced with cyclopropane and the baby intubated. Decamethonium 0.5 mg plus "Wydase" 0.5 ml was injected intramuscularly, and anaesthesia continued with twenty per cent cyclopropane. Respiration continued, but was obviously depressed after five minutes and it remained so for a further fifteen. Relaxation was good. Twenty-five minutes after injection of the relaxant the operation was over and the child was opening his eyes.

The second patient was a baby of 13 lb. (6 kg) for reduction of an intussusception. Premedication and induction were as in the previous case. Decamethonium 0.5 mg plus Wydase 0.5 ml was injected intramuscularly; 4 minutes later the baby was still breathing so another identical dose of relaxant with hyaluronidase was given. In 2 minutes there was apnoea and anaesthesia was continued with nitrous oxide and oxygen. After a quarter of an hour respirations returned and cyclopropane was reintroduced. Thirteen minutes later the abdomen, on closure, was still lax, but at the end of the operation, three-quarters of an hour after the first injection of relaxant, there was no evidence of its action and the child was opening his eyes.

I think that there is a place for decamethonium iodide in anaesthesia for infants. The weight/dose relationship in the above cases indicates that they are relatively resistant to its action.

SUMMARY

(1) Since a brief period of popularity following its introduction in 1949, decamethonium iodide has been used progressively less by anaesthetists. The evidence for this is presented and the reasons

discussed. The principal of these is that too great an emphasis has been placed on its disadvantages, which have been exaggerated and misrepresented in the minds of the majority of anaesthetists.

(2) Pharmacological points of importance to the use of decamethonium in anaesthesia, including its relation to neostigmine, are described.

(3) Indications for the use of decamethonium iodide in anaesthesia are discussed. It is a reliable relaxant for many of the shorter surgical procedures. Its use for Caesarean section and in infants is described.

ACKNOWLEDGMENT

I wish to thank Dr. Wm. Shearer for his helpful criticism of this paper.

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AUTOMATIC NON-REBREATHING VALVE

BY

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EFFICIENT ventilation of the anaesthetized patient, without carbon dioxide absorption, can be carried out using the valve to be described. It is simple, reliable, efficient and silent.

In figure 1 A and E are low resistance valves. P_1 and P_2 form a bypass opening into the balloon B, which lies free in the exit tube X. The balloon is made of very thin rubber and is of such a size that when inflated without any distension of its wall it completely occludes the exit tube. When collapsed it offers negligible resistance to expiration. T is a three-way tap which if desired will close P_1 and open P_2 to the atmosphere. The dotted lines indicate that the reservoir bag and the proximal end of the bypass may be placed anywhere between the gas machine and valve A.

The valve in use.

(*a*) During controlled or assisted respiration, pressure on the reservoir bag causes the balloon B to fill the exit tube, all the fresh gases passing into the patient's lungs. When the pressure is removed, the balloon collapses and the expired gases pass out through the exit tube.

(*b*) When the patient is breathing unaided, the balloon remains deflated throughout the cycle, unless the minute volume delivered from the machine exceeds that of the patient. In that case pressure rises in the system and ultimately the balloon will occlude the exit tube. To obviate the difficulty of adjusting the flow of gases exactly to match the patient's minute volume, the balloon may be vented to atmosphere and the bypass closed by tap T. The gas flow may then be set at a figure in excess of the patient's minute volume. This is particularly desirable where a facepiece is being used.

Dimensions.

Internal diameter of exit tube X 1 inch (2.5 cm)
" " bypass P_1 and P_2 $\frac{5}{16}$ " (8mm)
Deadspace approx. 10 ml

Resistance.

(*a*) Inspiration:	Flow rate litres/min	Pressure drop mm H_2O
	30	5
	40	8
	50	12
	60	14

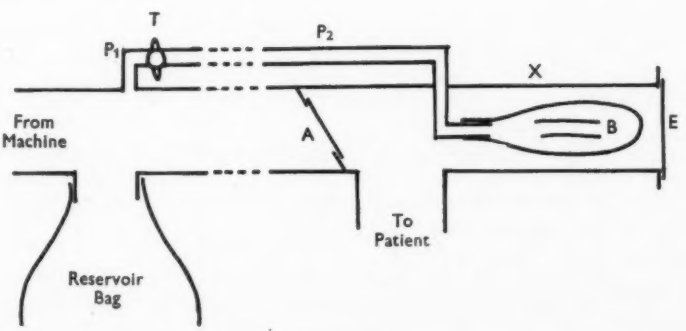

FIG. 1

(*b*) Expiration:

Flow rate litres/min	Pressure drop mm H_2O
30	8
40	10
50	12
60	13

When controlled or assisted respiration is to be used throughout a case then the expiratory valve may be fixed widely open if so desired. This reduces the expiratory resistance to the low figure of 5 mm H_2O at 60 litres/min.

Any pattern of inspiration can be produced in the apnoeic patient. The reservoir bag must be completely released at the end of inspiration.

The valve responds instantly to the slightest inflation pressure. During controlled and assisted respiration the loss of fresh gas is approximately 5 per cent.

The valve has been in use for nearly twelve months and has proved completely reliable. The original balloon is still in use.

DISCUSSION

Ventilation of the apnoeic anaesthetized patient with mixtures of nitrous oxide and oxygen is usually effected either by a carbon dioxide absorbing system, circle or to-and-fro, or less efficiently by the ordinary "semi-closed" set-up. In both cases the excess gases are vented through a controlled leak simultaneously with the inspiratory stroke. It is sometimes difficult, especially for the inexperienced, to assess the actual amount of gaseous mixture entering the lungs. Degrees of resistance to inflation can also be difficult to appreciate.

The valve described provides a positive method of inflation. It will be noted that in all circumstances accurate control may be exercised over the patient's minute volume, thus helping to avoid the dangers of both over- and underventilation.

Enquiries should be addressed to: Medical and Industrial Equipment Ltd., 12 New Cavendish Street, London, W.1.

ROYAL COLLEGE OF SURGEONS OF ENGLAND
FACULTY OF ANAESTHETISTS

Scientific Meeting . . . June 14, 1958

SHOCK AND ALLIED PHENOMENA

10.00 a.m.	Opening.
10.15—10.30 a.m.	Sir Henry Dale, O.M., G.B.E., F.R.C.P., Hon. F.R.C.S., F.R.S.
10.30—11.15 a.m.	"The Pharmacological Aspects of Shock": Prof. W. D. M. Paton, F.R.S.
11.15—11.45 a.m.	COFFEE
11.45—12 noon	Dr. J. B. Wyman, M.B.E., F.F.A.R.C.S.
12.00—12.30 p.m.	"Adrenocortical Shock in Surgery": Dr. R. I. S. Bayliss, F.R.C.P.
12.30—2.00 p.m.	LUNCH
2.00—2.50 p.m.	"Diagnosis, Prevention and Treatment of 'Wound Shock'": Mr. Ruscoe Clarke, F.R.C.S.
2.50—3.30 p.m.	"Trauma, Shock and the Anaesthetist": Dr. L. J. Wolfson, F.F.A.R.C.S.
3.30—4.00 p.m.	TEA
4.00—4.30 p.m.	"Some Advances in the Transport of Ill and Injured Patients": Dr. R. I. Bodman, F.F.A.R.C.S.
4.30—5.00 p.m. (approx.)	Film: "Cardiac Arrest". This film has been made by I.C.I. with the advice of Dr. A. J. W. Beard, F.F.A.R.C.S., acting on behalf of the Board of Faculty.

ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

JOHN SNOW, M.D.

Licentiate of the Royal College of Physicians

(*Continued from page* 201)

Hare-Lip. I have notes of 147 operations for hare-lip, for which I have given chloroform. A few of these operations were performed by Mr. Arnott, Mr. Cæsar Hawkins, Mr. Bowman, Mr. Henry Charles Johnson, and others, but nearly nine-tenths of the whole number were performed by Mr. Fergusson, either in his private practice or in King's College Hospital. A great number of Mr. Fergusson's operations were in children from three to six weeks old; and some were younger than this, one being only eight days. There used to be an objection against operating for hare-lip on the very young infants, as it was said that they often died of convulsions, which I believe to be true. The convulsions were supposed to be caused by the shock of the operation on the nervous system, which I believe to be entirely untrue. I believe they were caused by hæmorrhage; and I would not recommend the surgeon to perform his first operations for hare-lip on very young and feeble infants. The great success of this operation of late years, in the first weeks of life, depends on the dexterity of the surgeon who performs the operation so quickly that scarcely any blood is lost. When Mr. Fergusson performs this operation, the infant is held by a nurse, who is seated opposite to him, whilst its head is placed in his own lap between his thighs. An assistant compresses the labial artery on the right side, by grasping the lip between his finger and thumb, just at the angle of the mouth; a sharp-pointed scalpel is pushed through the lip on the right side, just below the nose, and carried downwards so as to cut away the edge of the fissure; then the same performance is done on the left side of the fissure, while Mr. Fergusson compresses the labial artery on that side with the finger and thumb of his left hand. In about twenty seconds from the beginning of the operation, the hare-lip pins are introduced, and the cut edges of the lip being pressed together, the bleeding is at once entirely stopped. I have no doubt that many lives are saved by early operation, especially amongst the poor, as a child with a bad hare-lip cannot take the breast till it is operated on, and there is a very great mortality amongst infants brought up by hand.

The blood which escapes when the infant is laid on its back flows back into the throat, and it usually passes on each side of the epiglottis, and runs into the stomach without any act of deglutition. In a few cases of strong children, in whom the bleeding is rather free, the breathing gets embarrassed, and Mr. Fergusson turns the face of the child downwards for a moment to let the blood run out of its mouth. When

the quantity of blood flowing into the throat is greater than can run down into the stomach, in the way I have mentioned above, the glottis closes and the breathing stops, which gives the indication for turning the face downwards. I have seen a few operations in the hospital for hare-lip, without chloroform, whilst the children were on their backs. In these cases they cried violently from the pain, set the blood in the mouth into violent commotion, and then drawing a deep inspiration, drew a little of the blood into the larynx, which caused a violent cough; so that there was usually much more appearance of choking than in the cases where chloroform was given. Moreover, in these latter cases, it is usually towards the end of the operation that the children sometimes become embarrassed with the blood; not because the quantity of blood is greater, but because the sensibility is returning. I have seen one case which shows that the effects of chloroform, when deep or long-continued, will diminish the sensibility of the glottis. After an infant was made insensible some years ago for an operation for hare-lip, it was found that an instrument for dividing the projecting intermaxillary bone was wanting, and I kept the child insensible for several minutes, by administering chloroform occasionally, until the instrument was found; the bleeding was rather free, and some of it entered the windpipe and caused a tracheal râle. The child coughed it up on awaking, and no ill consequences followed; but the occurrence confirms the opinion previously expressed, that the insensibility should not be both deep and long-continued at a time when copious hæmorrhage is flowing into the throat. The effects of chloroform pass off very quickly in infants, and it is not often that they last till the operation of hare-lip is finished, short as that operation is. In private practice, indeed, when the parents of the infant are close by, I usually have an opportunity to apply a little chloroform, mixed with spirit, on a sponge, in the course of the operation, when it is required to prevent crying; but in the hospital, the children sometimes cry a little before the operation is concluded.

Cancer of the Lip. I have memoranda of nineteen cases of cancer of the lower lip, and three or four of the upper lip, in which I have administered chloroform. As there is never an easy chair in the operating theatre of an hospital, and it is difficult to keep the patient in a common chair when he is under the influence of chloroform, it is better to place the hospital patient on the operating table, with his head and shoulders raised during this operation; but in private practice the patient may either be placed on a sofa, or in a large easy chair with a high back. The effect of the chloroform often lasts to the end of the operation, if it be completed within two or three minutes; but I always go provided with a hollow sponge, and a mixture of chloroform and spirit to apply during the operation, if required.

Division of the Sensory Nerves of the Face. I have notes of nineteen cases in which I have administered chloroform during this operation. They were chiefly performed by Mr. Fergusson, but a few of them by Mr. Bowman. The operation is of so painful a nature, that I believe it was seldom performed before the practice of inhaling narcotic vapours was introduced. It is done subcutaneously, by means of a small sharp-pointed bistoury,

by which the affected nerves are chopped up by twenty or thirty incisions, at and near the points where they issue from their respective foramina. In operating on the mental branch of the fifth nerve, the bistoury is sometimes introduced from the face, and sometimes from the interior of the mouth. The pain continues for two or three days, till the inflammation caused by the operation subsides, when there is usually a complete absence of pain for three or six months, at the end of which time the operation has often to be repeated. I am not aware whether the relief has been permanent in any case, but it has often been very complete for a time. One patient, on whom Mr. Fergusson operated in King's College Hospital, looked like an old man at the time of the operation, but this was the effect of his severe suffering; for a week or two afterwards he looked his real age, which I think was less than forty. This operation is not performed for the milder cases of neuralgia, or for cases that can be cured by quinine or iron; but only for the more terrible forms of the complaint, which fortunately are somewhat rare. Rare as they are, however, they occur sometimes in near relatives.

Division of other Nerves of Sensation. I have notes of nine cases in which nerves in other parts of the body were divided, and a portion cut out, for neuralgia. On four occasions the nerve was situated in a stump following amputation; and on two occasions a tumour of the nerve was removed. The operations were performed by Mr. Fergusson, Mr. Solly, and Mr. Paget.

Operations on the Eye. The operations for cataract are frequently performed without chloroform, when the patient has sufficient resolution to keep his eye steady. I have, however, administered chloroform fifty-three times during the extraction of cataract; thirty of the cases occurred in the private practice of Mr. Bowman. On November 25th, 1851, I administered chloroform whilst Mr. White Cooper extracted a piece of flint from the interior of the eye; and on February 7th, 1852, whilst Mr. Bowman extracted the capsule of the lens. On February 17th of the same year, I assisted Mr. White Cooper with chloroform whilst he extracted a cataract from the eye of an elderly lady; and I assisted him in eleven other cases during that and the following year. I assisted Mr. George Pollock in two operations of the extraction of cataract in June 1852; and Mr. Lawrence in three operations in 1853. Eighteen of Mr. Bowman's operations were performed in the summer and autumn of 1854, and were of the usual kind; but in six out of the twelve cases in which I have since assisted him, the cataract was first drilled and then removed, in a softened state, through a small opening in the cornea, by means of a small scoop. I have assisted Mr. Alexander in two cases, and Mr. Critchett also in two. Several of the patients were over eighty years of age.

The operation for the extraction of cataract is said not to be a painful one, but the patient requires to be as insensible during its performance as if he were about to undergo lithotomy, or a great amputation; without this, the eye and eyelids will not be steady. The insensibility must be kept up completely until the cataract is extracted.

It is necessary that the stomach should

be empty when the patient inhales chloroform for this operation, in order that vomiting may, if possible, be avoided. There was a little vomiting in a very few of the cases in which I administered chloroform, but it was not attended with straining, and I believe it did no harm in any case. Mr. Bowman informed me of a case of his in which chloroform was administered in the Ophthalmic Hospital for the extraction of cataract, and the woman vomited violently afterwards, and the eye was destroyed. She, however, was a person of bad constitution, and the vomiting might have occurred without the chloroform. The patients were lying on a sofa in all the operations, except, I think, one by Mr. Alexander.

I have notes of nine cases of the drilling of cataract in which I have administered chloroform, and there were some other cases in 1848, of which I have no memoranda. Some of the early operations were performed by Mr. George Pollock, and the more recent ones by Mr. Bowman. Many of the patients were infants or children. There have been two cases of the removal of coagulated lymph from the interior of the eye, by Mr. Bowman and Mr. White Cooper; and six cases of the formation of artificial pupil, by the same surgeons, and Mr. Dixon; and in two cases lately, Mr. Bowman has removed a portion of the iris.

I have given chloroform in 25 cases of excision of the eyeball; 20 of the operations have occurred within the last two years, in addition to some in which I administered amylene. The whole of the operations were performed by Mr. Bowman, except one by Mr. Fergusson, and one by Mr. Hancock. The operation is of late years a much less formidable one than formerly, owing to the plan of commencing to dissect off the conjunctiva just around the cornea. After the eyeball is removed, the edges of the conjunctiva are drawn together by a fine suture, so that scarcely any wound is left, and the patient can generally begin to wear an artificial eye in four or five days. In cases of malignant disease extending beyond the globe, of course, the more formidable and extensive operation would still require to be performed.

I have administered chloroform for the removal of sparks of iron and other foreign bodies from the cornea, chiefly in cases in which the surgeon had previously tried without success. Under the influence of chloroform, the foreign matters were always removed very readily. There have also been operations for the removal of growths from the eye and granular growths from the conjunctiva, and also for staphyloma and pterygion.

I have memoranda of 54 operations for strabismus in which I have administered chloroform. The greater number of them were performed by Mr. Bowman, but several by Mr. Fergusson, and a few by other surgeons. One operation was performed by the late Mr. Dalrymple. Mr. Bowman generally operates on both eyes at the same time. A great number of the patients who have taken chloroform for this operation were children. They have nearly all been lying down during the operation.

There have been nine operations for ectropion and entropion, chiefly by Mr. Bowman. I have administered chloroform on four occasions whilst Mr. Bowman has performed a plastic opera-

tion for the formation of a new eyelid. On three occasions the eyelid had been destroyed by a burn, and the material for the new one was taken from the integuments of the forehead. The operations were necessarily tedious.

Removal of Foreign Bodies and Polypi from the Ear. In May 1849, Mr. Henry Charles Johnson extracted a pea from the ear of a child, six years of age. The pea had been a month in the ear, and Mr. Johnson had endeavoured to examine the ear without chloroform, but could not do so. In May 1857, I administered chloroform to a child aged three years, a patient of Mr. Tuach, whilst Mr. Hewett extracted a glass bead with sharp edges from the ear. He got it out with a director. I have notes of four cases in which a polypus was removed from the ear by Mr. Partridge, Mr. Fergusson, Mr. Henry Lee, and Mr. Henry Smith; and I recollect giving chloroform more than once at Mr. Toynbee's whilst he performed a similar operation, although I have no memoranda of the circumstances.

The Removal of Polypi and Foreign Bodies from the Nose. I have memoranda of fourteen cases in which I have administered chloroform for the removal of polypi from the nose. The operations were nearly all performed by Mr. Fergusson. The patient was nearly always seated in an easy chair, and the chloroform, in several cases, was repeated to keep up the insensibility till the operation should be completed. In one of the cases, the polypus caused a protusion of the nasal bones; the nostril was slit up, and there was very great hæmorrhage as the polypus was brought away. The pulse became small for a time, but there was no syncope. The patient did well. In June 1852, I gave chloroform to a girl, five years old, and Mr. Fergusson scooped out some polypus growth from the right nostril, and also an oval softened body, rather bigger than a horse-bean, which was a young orange that the child had pushed up her nose in India. The case had given rise to a good deal of difference of opinion amongst medical men in India and Malta, who generally discredited the child's account of the orange. In August 1856, Mr. Stanley removed a bean from the nose of a child.

Certain Operations in the Mouth. I have notes of six operations for cancer of the tongue, performed by the late Mr. Keate, Mr. Quain, Mr. Hancock, and Mr. Paget. Mr. Paget's was a case of epithelial cancer, in a lady, about twenty-five. The operation was one of excision of the tumour, and I lately heard that the patient remained free from the complaint. The other operations were by ligature. Mr. Quain's was a hospital patient, and I do not know the ultimate result of the case. The other patients had a return of the disease, and died after great suffering.

I have notes of ten operations for epulis, chiefly by Mr. Fergusson. The patient was generally on a sofa or the operating table, with the head and shoulders raised. As the operations were soon completed, the chloroform seldom required to be repeated. There have been some cases of cancerous disease of the gums and alveolar process in which I have administered chloroform. One of these was a patient of Mr. Bell, the dentist, on whom Mr. Hilton operated. I assisted the late Mr. Avery by giving chloroform in two operations for cleft palate. A large cork with a string to

it* was kept between the molar teeth on one side during the operation; and the inhalation was repeated from time to time. The surgeon, however, much prefers to have the patient awake during this operation, when he can get his assent.

I have administered chloroform four times for the removal of the tonsils. Three times in children, and once in the adult. In the case of a child on which Mr. Curling lately operated, he removed one of the enlarged tonsils very easily and very well, but just as he was beginning to remove the other, the child began to vomit its breakfast, and the throat was afterwards so filled with mucus and blood, that we thought it better to defer the remainder of the operation till another day.

Plastic Operations. I have memoranda of 50 plastic operations in which I have administered chloroform, in addition to those on the eyelids, previously mentioned. Eight of the operations were for the formation of a new nose. Five of them were by Mr. Fergusson, two by Mr. Critchett when Mr. Fergusson was present, and one by Mr. Samuel A. Lane. I made the patients insensible with the inhaler before the operation was commenced, and afterwards kept up the insensibility by means of chloroform, diluted with spirit, on a hollow sponge. No fewer than 24 of the plastic operations were for the remedy or mitigation of deformity caused by burns. In fourteen of these cases, the operation was performed on the neck, but often extended to the breast and lower part of the face. The other ten operations were for burns on the face and arms and other parts of the body. Nearly all these operations were performed by Mr. Fergusson. One of his patients was a gentleman from New York, who had a most severe burn in the face when a child. The operations, without the action of a narcotic, would be of the most painful nature; and the greater number of those at which I have been present would not have been performed, except for the discovery of narcotism by inhalation. The remaining eighteen plastic operations were for a variety of purposes, such as replacing the loss of a lip, the closing of artificial anus, and of openings in the cheek, and a variety of other defects, either congenital, or arising from injury or disease. They were nearly all performed by Mr. Fergusson.

(To be continued)

* I never allow of a cork or any such substance being put into a patient's mouth when insensible unless it is well tied to a string, lest it should be swallowed.

CATALOGUE OF MEDICAL FILMS

Imperial Chemical Industries Ltd. have issued a further edition of their catalogue of medical films. They are all 16mm sound films and have been produced in collaboration with specialist units throughout the country. Many of the films listed have been available for some years. The black-and-white series on the techniques of anaesthesia are suitable for inclusion in an undergraduate teaching programme. Recent additions are colour films on various physiological topics of interest to anaesthetists. The catalogue gives details of the subjects and also running times. These films are available to "approved medical audiences only", and no charge is made to borrowers of I.C.I. films, except for return carriage. Further details may be obtained from the I.C.I. Film Library, Imperial Chemical House, Millbank, London, S.W.1.

Ian C. Geddes

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